PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 489/02, A61K 31/485	A1	**(11) International Publication Number:** WO 96/16063 **(43) International Publication Date:** 30 May 1996 (30.05.96)

(21) International Application Number: PCT/GB95/02712

(22) International Filing Date: 20 November 1995 (20.11.95)

(30) Priority Data:
9423542.1 22 November 1994 (22.11.94) GB

(71) Applicant *(for all designated States except US)*: BRITISH TECHNOLOGY GROUP LIMITED [GB/GB]; 101 Newington Causeway, London SE1 6BU (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: MARPLES, Brian, Arthur [GB/GB]; 4 Berkerley Road, Loughborough, Leicestershire LE11 3SJ (GB). TRAYNOR, John, Richard [GB/GB]; 357 Beacon Road, Loughborough, Leicestershire LE11 2RA (GB).

(74) Agent: PERCY, Richard, Keith; British Technology Group Limited, Patents Dept., 101 Newington Causeway, London SE1 6BU (GB).

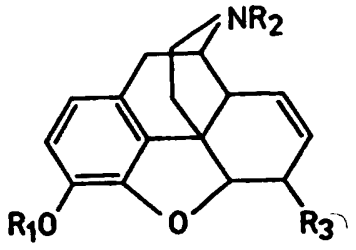
(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

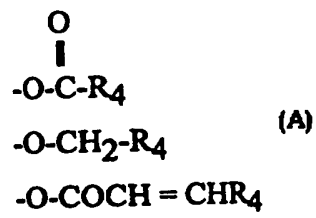
(54) Title: MORPHINE AND CODEINE DERIVATIVES FOR USE IN THERAPY

(57) Abstract

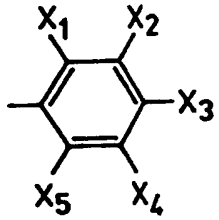
A compound of formula (I) wherein R_1 = H (morphine analogue), CH_3 (codeine analogue), R_2 = H, alkyl group of 1 to 4 carbon atoms, allyl, cyclopropylmethyl, R_3 = a group (A), $-O-CH_2-R_4$ (ether), $-O-COCH=CHR_4$ (cinnamate), R_4 = (B), wherein X_1, X_2, X_3, X_4 and X_5 which may be the same or different are separately selected from H, alkyl f 1 to 4 carbon atoms, NH_2, NO_2, alkoxy group of 1 to 4 carbon atoms, hydroxy, halogen, N-alkyl, group of 1 to 4 carbon atoms, morpholine, or a group COR_5 wherein R_5 is H, OH, O-alkyl where alkyl is from 1 to 4 carbon atoms, or one of X_1 and X_2, X_2 and X_3, X_3 and X_4 or X_4 and X_5 together with an alkylene group optionally interrupted by O, S or N of up to 5 atoms in length complete a ring and a pharmaceutically acceptable salt thereof for use in therapy.



(I)



(A)



(B)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CS	Czechoslovakia
CZ	Czech Republic
DE	Germany
DK	Denmark
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgystan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakhstan
LI	Liechtenstein
LK	Sri Lanka
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SI	Slovenia
SK	Slovakia
SN	Senegal
TD	Chad
TG	Togo
TJ	Tajikistan
TT	Trinidad and Tobago
UA	Ukraine
US	United States of America
UZ	Uzbekistan
VN	Viet Nam

MORPHINE AND CODEINE DERIVATIVES FOR USE IN THERAPY

Field of the invention

This invention is in the field of novel morphine-6-glucuronate and codeine-6-glucuronate analogues and their use in therapy as opioid analgesic agents.

Background to the invention

Description of the prior art

While opium has been used for centuries to control pain, it was only in the mid-1920's that the structure of the principle active alkaloid, morphine was established.

The opioid analgesic morphine is often the drug of choice for terminally ill cancer patients and in other cases of severe pain. Although traditionally used by the intramuscular route, other routes of administration, particularly the oral administration of morphine is becoming more widespread. One of the drawbacks however to the use of orally administered morphine is a variable absorption and metabolism of the morphine by individual patients due to extensive hepatic metabolism and poor bio-availability which results in an unpredictive effectiveness. Additionally, it is well known that the therapeutic use of morphine gives rise to various side effects such as respiratory depression, nausea, vomiting, abuse potential etc.

Despite these disadvantages, morphine is still often the analgesic of choice and its use is generally increasing.

It has been reported that metabolites of morphine such as morphine-6-glucuronide (M6G) may be as or more active than the parent drug with less chance of side effects. Osborne et al.(1988), The Lancet, April 6, p 828 has discussed the use of morphine-6-glucuronide as a drug substance in its own right.

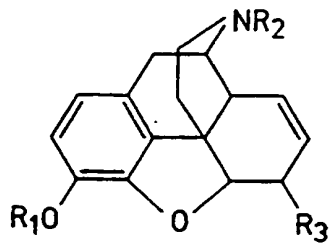
In animals, morphine-6-glucuronide is a more potent antinociceptive agent than morphine, the exact relationship depending on the test model and route of administration, but always being more potent when administered by the intrathecal route. Nevertheless, the physicochemical characteristics of morphine-6-glucuronide restricts any potential oral administration and hence reduces its clinical usefulness. It is thus desirable to identify

other derivatives of morphine which preserve the pharmokinetic advantages of morphine-6-glucuronide but with improved oral bioavailability for their properties as analgesic agents.

Summary of the invention

The inventors have identified and synthesised 6-substituted derivatives of morphine and codeine, another opioid analgesic compound.

Accordingly the invention provides a compound of Formula I below



wherein

R_1 = H (morphine analogue), CH_3 (codeine analogue)

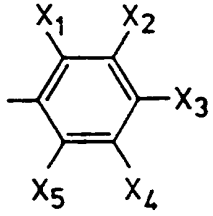
R_2 = H, alkyl group of 1 to 4 carbon atoms, allyl, cyclopropylmethyl

R_3 = a group $-O-\overset{\overset{O}{\|}}{C}-R_4$

$-O-CH_2-R_4$ (ether)

$-O-COCH = CHR_4$ (cinnamate)

wherein R_4 =

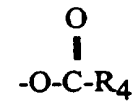


wherein X_1, X_2, X_3, X_4 and X_5 which may be the same or different are separately selected from H, an alkyl group of 1 to 4 carbon atoms, NH_2, NO_2, alkoxy group of 1 to 4 carbon atoms, hydroxy, halogen, N-alkyl group of 1 to 4 carbon atoms, morpholine, a group COR_5 wherein R_5 is H, OH, O-alkyl where alkyl is from 1 to 4 carbon atoms, or one of X_1 and X_2, X_2 and X_3, X_3 and X_4 or X_4 and X_5 together with an alkylene group optionally interrupted by O, S or N of up to 5 atoms in length complete a ring and a pharmaceutically acceptable salt thereof for use in therapy.

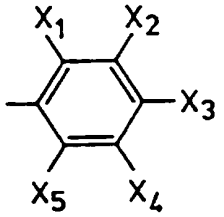
Description of the preferred embodiments

Morphine and other traditional opiate analgesics act through opioid μ receptors to induce analgesia together with the well known side effects of addiction, respiratory depression etc., whilst opioid κ receptors may mediate psychomimetic and other effects. It is known that the opioid receptor profile of morphine and morphine-6-glucuronide differ. The compounds of the present invention exaggerate this difference resulting in compounds which have an equivalent μ-affinity, a higher δ-affinity and a lower κ-affinity. Hence the compounds of the invention are more beneficial than M6G, by being as well as more bio-available, having reduced κ-mediated side effects.

Of all the compounds in the above Formula I the preferred morphine (R_1 = H) and codeine (R_1 = CH_3) derivatives are those wherein R_2 is H, an alkyl group of 1 to 4 carbon atoms, preferably methyl or allyl (thus forming nalorphine-type derivatives). R_3 is preferably a grouping



and R_4 is preferably a group



wherein X_1, X_2, X_3, X_4 and X_5 are H, NH_2, NO_2, OH, halogen or COR_5 where R_5 is

OH. In all cases, when the compound of the invention contains an alkyl group, this may be linear or branched.

In the above compounds preferably at least 3 of X_1, X_2, X_3, X_4 and X_5 are H. Where there are substituents, the substituents may be in the ortho, meta or para positions but where there is only one substituent preferably this is in the ortho position, more preferably in the para position and where there is more than one substituent, one is in the para position. Where there is an alkylene ring formed by two of X_1, X_2, X_3, X_4 and X_5, preferably this is between X_2 and X_3 or X_3 and X_4. It may be, for example a group $-O-CH_2-O$.

Of all the compounds embraced by Formula I, the preferred compounds are morphine or codeine-6-nitrobenzoate, morphine or codeine-6-hydroxybenzoate and morphine or codeine-6-phthalate.

As stated above, the morphine-6-glucuronide analogues and codeine-6-glucuronide analogues are believed to function as analgesic agents. Thus, the invention further provides a pharmaceutical composition which comprises a compound of Formula I together with a pharmaceutically-acceptable diluent or carrier, preferably one which is sterile and pyrogen free. As indicated, the compounds may be formulated as salts formed with physiologically acceptable inorganic or organic acids and when so formulated it is preferred to use methane sulphonic acid, isethionic acid, tartaric acid or another solubilising acid.

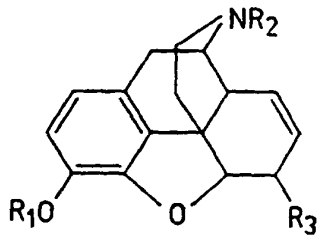
The compounds of Formula I may be formulated singly or as a mixture of two or more compounds for use as pharmaceuticals by a variety of methods. The composition may be in a form suitable for oral administration as a tablet or capsule or liquid medicine, a suppository or in a form suitable for parenteral administration by for example injection or infusion, as a sterile solution or infusion. The compounds may be formulated for controlled delayed release, e.g. in tablets and suppositories.

Pharmaceutical compositions containing compounds of Formula I may be formulated in unit dosage form, i.e. in the form of discrete portions, each containing a unit dose or a multiple or sub-multiple of a unit dose.

Without limitations to dosages it may be stated that the compound of Formula I will normally be administered to a warm-blooded animal at a dose within the range for example in man of 1-100 mg orally more preferably 5-50 mg orally or by intramuscular or

subcutaneous injection up to 6 times daily. As a general guide, the dosage used will be equivalent to or slightly less than dosages of morphine or codeine which are well characterised and known to a person skilled in the art. It will be appreciated however that the specific dosage for a patient will depend on how much pain that patient is experiencing and actual dosages in this case will be determined by the attending medical staff.

It is believed that most of these compounds are novel, thus, according to a further aspect of the invention there is provided a compound of Formula II.



wherein

R_1 = H (morphine analogue), CH_3 (codeine analogue)

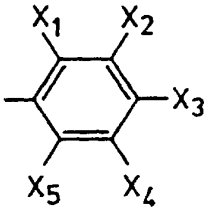
R_2 = H, alkyl group of 1 to 4 carbon atoms, allyl, cyclopropylmethyl

R_3 = a group $-O-\overset{O}{\overset{\|}{C}}-R_4$

$-O-CH_2-R_4$ (ether)

$-O-COCH=CHR_4$ (cinnamate)

wherein R_4 =



wherein X_1, X_2, X_3, X_4 and X_5 which may be the same or different are separately selected

from H, an alkyl group of 1 to 4 carbon atoms, NH_2, NO_2, alkoxy group of 1 to 4 carbon atoms, hydroxy, halogen, N-alkyl group of 1 to 4 carbon atoms, morpholine, a group COR_5 wherein R_5 is H, OH, O-alkyl where alkyl is from 1 to 4 carbon atoms, or one of X_1 and X_2, X_2 and X_3, X_3 and X_4 or X_4 and X_5 together with an alkylene group optionally interrupted by O, S or N of up to 5 atoms in length complete a ring with the proviso that not all X_1, X_2, X_3, X_4 and X_5 are hydrogen and pharmaceutically acceptable salts thereof.

The novel morphine-6-glucuronide analogues and codeine-6-glucuronide analogues of the invention may be prepared by any process known to be applicable to the preparation of chemically related compounds. Accordingly, such processes form a further feature of the invention.

In particular, the codeine-6-benzoate derivatives for example may be synthesised from codeine by reaction with the appropriate acid anhydride or acid chloride in the presence of dimethylammino pyridine (DMAP). Protection of the 3-hydroxy functions of morphine as the 3-t-butyldimethylsilyl (3-t-BDMS) ether allows synthesis of the corresponding morphine analogues after deprotection of the 3-t-BDMS-6-esters with tetrabutylammonium fluoride (TBAF).

As a further example morphine and codeine-6-ethers may be prepared by the reaction of codeine or similarly protected morphine with the appropriate alkyl chloride in the presence of sodium hydride in THF.

According to a further aspect of the invention there is provided a method of alleviating pain in an individual in need of such treatment which comprises administering to said individual a therapeutically effective amount of a compound of Formula I or II as defined hereinbefore. The invention also provides the use of a compound of Formula I or II as defined hereinbefore in the manufacture of a novel medicament for use in alleviating pain.

The invention is illustrated by the following Examples in which

Figure 1 referred to illustrates pathways for the synthesis of codeine analogues;

Figure 2 referred to illustrates pathways for the synthesis of morphine analogues.

EXAMPLE 1: SYNTHESIS OF CODEINE ANALOGUES OF M6G

The syntheses f the compounds described in this Example are shown schematically in Figure 1.

Preparation of 7,8-Didehydro-4,5a-epoxy-3-methoxy-17-methyl-6a-succinyloxy-morphinan (1)

A mixture of codeine (1 g, 3.34 mmol) and succinic anhydride (2g, 20 mmol) in pyridine (5 cm^3) was refluxed for 1 hr. The hot reaction mixture was poured onto ice and the resulting white precipitate collected on a filter. The precipitate was washed with cold water. Crystallisation from DCM-petroleum ether gave the ester **(1)** (240 mg, 18%) m.p. 154-6°C; ν_{max}(nujol)/cm^{-1} 3432 (OH), 1720 (C=O ester), 1632 (C=O acid); δ_H($CDCl^3$) 1.89 (1 H, d, J 13.5, 15e-H), 2.39-2.79 (11 H, m, NMe, 16-H_2, 19-H_2, 20-H_2, 10α and 15a-H), 3.01 (1 H, d, J 19, 10β-H), 3.11 (1 H, t, J 2.5, 14-H), 3.76 (1 H, q, J 3, 9-H), 3.86 (3 H, s, OMe), 5.15 (1 H, d, J 6.5, 5-H), 5.28 (2 H, m, 6 and 8-H), 5.60 (1 H, d, J 10, 7-H), 6.55 and 6.68 (2 H, ABq, 1 and 2-H); m/z 399 (M^+ 13%) 299(100), 282(22), 229(29), 188(14), 162(31), 124(27), 70(17), 56(56), 42(49).

Preparation of 6a-(2-Carboxybenzyloxy)-7,8-didehydro-4,5a-epoxy-3-methoxy-17-methyl-morphinan (2)

A mixture of codeine (1 g, 3.34 mmol) and phthalic anhydride (2 g, 13.5 mmol) in pyridine (5 cm^3) was refluxed for 1 hour. The hot reaction mixture was poured onto ice and the resulting white precipitate collected on a filter. The precipitate was washed with cold water Crystallisation from DCM-petroleum ether gave the ester **(2)** (2.67 g, 88%) m.p. 227-8°C (decomp);

ν_{max}(nujol)/cm^{-1} 3417 (OH), 1713 (C=O ester), 1608 (C=O acid); δ_H($CDCl_3$) 1.98 (1 H, d, J 13.5, 15e-H), 2.68-2.97 (7 H, m, NMe, 10α, 15a, 16-H and OH), 3.07 (1 H, d, J 19, 10β-H), 3.44 (1 H, d, J 7, 16-H), 3.59 (1 H, t, J 2.5, 14-H), 3.85 (4 H, m, OMe and 9-H), 5.44 (3 H, m, 5, 6 and 8-H), 5.80 (1 H, d, J 8.5, 7-H), 6.61 and 6.74 (2 H, ABq, 1 and 2-H), 7.37 (1 H, t, J 7.5, 21-H), 7.51 (1 H, t, J 7.5, 22-H), 7.67 (1 H, d, J 7.5, 20-H), 8.04 (1H, d, J 7.5, 23-H); δ_C 21.40, 32.09, 36.84, 40.80 (NMe), 40.96, 47.31, 56.99 (OMe), 60.11, 67.66, 87.38, 115.40, 119.88, 122.83, 126.79, 127.29, 127.90, 129.75,

129.98, 130.22. 131.16, 131.39, 132.07, 143.26, 146.81, 166.68, 175.83;
m/z 447 (M^+) 299(100), 282(10), 229(14), 148(7), 124(11), 104(33), 76(19).
[FAB-MS, Found ($M+H^+$): 448.1752. $C_{26}H_{26}NO_6$ requires 448.1760].

Preparation of 6a-Benzoyloxy-7,8-didehydro-4,5a-epoxy-3-methoxy-17-methyl-morphinan (3)

To a solution of codeine (300 mg, 1 mmol) in pyridine (3 cm^3), under nitrogen, was added benzoyl chloride (0.35 ml, 1 mmol) and the reaction stirred at room temperature for 4 hours. DCM (10 ml) was added and the solution washed with a 5% $CuSO_4$ solution and water, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 5% MeOH in DCM) to give the ester (3) (295 mg, 73%).

Alternatively a mixture of codeine (300 mg, 1 mmol), benzoic acid (122 mg, 1 mmol) and DMAP (122 mg, 1 mmol) in DCM was stirred for 1 hour at 0°C, the flask being fitted with a calcium chloride guard tube. DCC (230 mg, 1.1 mmol) was added and the solution, which was stirred at 0°C for 5 min before being allowed to warm up to room temperature, followed by stirring for a further 3 hours. The reaction mixture was washed successively with dilute HCl/water/bicarbonate/water, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 5% MeOH in DCM) to give the ester (3) (275 mg, 68%).

Recrystallisation in each case from DCM-petroleum ether gave crystals m.p. 130-132°C; ν_{max}(nujol)/cm^{-1} 1717 (C=O ester); δ_H($CDCl_3$) 1.91 (1 H, d, J 12.5, 15e-H), 2.12 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.37 (2 H, m, 10α and 16-H), 2.48 (3 H, s, NMe), 2.65 (1 H, dd, J 12.5, 4, 16-H), 2.86 (1 H, t, J 2.5, 14-H), 3.06 (1 H, d, J 18.5, 10β-H), 3.42 (1 H, q, J 3, 9-H), 3.72 (3 H, s, OMe), 5.20 (1 H, d, J 6.5, 5-H), 5.47 (2 H, m, 6 and 8-H), 5.78 (1 H, d, J 10, 7-H), 6.55 and 6.67 (2 H, ABq, 1 and 2-H), 7.43 (2 H, t, J 8, 21 and 23-H), 7.55 (1 H, t, J 8, 22-H), 8.09 (2 H, d, J 8, 20 and 24-H); δ_C 21.36, 35.09, 40.39, 42.50, 42.85 (NMe), 46.63, 56.79 (OMe), 59.08, 68.40, 87.95, 114.59, 119.13, 126.66, 128.13, 128.57, 129.31, 129.80, 130.63, 132.91, 142.10, 146.70, 165.92; m/z 403 (M^+, 53%) 282(28), 266(23), 229(14), 155(15), 122(31), 105(100), 77(51). (Found M^+, 403.1795. $C_{25}H_{25}NO_4$ requires 403.1783).

Preparation of 7,8-Didehydro-4,5a-epoxy-6a-(4-fluorobenzoyloxy)-3-methoxy-17-methyl-m rphinan (4 X=F in Figure 1)

To a solution of codeine (300 mg, 1 mmol) in pyridine (3 cm^3), under nitrogen, was added p-fluorobenzoyl chloride (0.35 cm^3, 477 mg, 3 mmol) and the reaction stirred at room temperature for 10 minutes. $CHCl_3$ was added and the solution washed successively with dilute HCl/water/bicarbonate/water, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 5% MeOH in $CHCl_3$) to give the ester **(4 X=F in Figure 1)** (403 mg, 95%). Recrystallisation from DCM-petroleum ether gave crystals m.p. 136-39°C; ν_{max}(nujol)/cm^{-1} 1717 (C=O ester); δ_H($CDCl_3$) 1.92 (1H, d, J 12.5, 15e-H), 2.16 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.42 (2 H, m, 10α and 16-H), 2.52 (3H, s, NMe), 2.75 (1 H, dd, J 12.5, 4, 16-H), 2.92 (1 H, t, J 2.5, 14-H), 3.08 (1 H, d, J 18.5, 10β-H), 3.53 (1 H, q, J 3, 9-H), 3.72 (3 H, s, OMe), 5.20 (1 H, d, J 6.5, 5-H), 5.43 (1 H, m, 6-H), 5.51 (1 H, d, J 10, 8-H), 5.77 (1 H, d, J 10, 7-H), 6.58 and 6.68 (2 H, ABq, 1 and 2-H), 7.11 (2 H, m, 21 and 23-H), 8.10 (2 H, m, 20 and 24-H); δ_C 20.63, 34.82, 39.98, 42.41, 42.60 (NMe), 46.60, 56.74 (OMe), 59.04, 68.41, 87.85, 114.49, 115.24, 115.59, 119.37, 126.36, 128.69, 129.26, 130.49, 132.43, 132.58, 142.30, 146.76, 165.05, 167.88; m/z 421 (M^+, 53%) 282(28), 266(23), 229(14), 155(15), 122(31), 105(100), 77(51).

(Found M^+, 421.1689. $C_{25}H_{24}NFO_4$ requires 421.1725).

Preparation of 6a-(4-Chlorobenzoyloxy)-7,8-didehydro-4,5a-epoxy-3-methoxy-17-methyl-morphinan (5 X=Cl in Figure 1)

To a solution of codeine (300 mg, 1 mmol) in pyridine (3 cm^3), under nitrogen, was added p-chlorobenzoyl chloride (0.38 ml, 527 mg, 3 mmol). The reaction mixture was stirred at room temperature for 10 min. EtOAc was added and the solution washed successively with dilute HCl/water/bicarbonate/water, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 10% MeOH in $CHCl_3$) to give the ester **(5 X=Cl in Figure 1)** (315 mg, 72%). Recrystallisation from DCM-petroleum ether gave crystals m.p. 165-67°C;

ν_{max} ($CHCl_3$) cm^{-1} 1719 (C=O ester); δ_H($CDCl_3$) 1.91 (1 H, d, J 12.5, 15e-H), 2.11 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.38 (2 H, m, 10α and 16-H), 2.49 (3 H, s, NMe),

2.65 (1 H, dd, J 12.5, 4, 16-H), 2.87 (1 H, t, J 2.5, 14-H), 3.07 (1 H, d, J 18.5, 10βH), 3.46 (1 H, q, J 3, 9-H), 3.72 (3 H, s, OMe), 5.19 (1 H, d, J 6.5, 5-H), 5.43 (1 H, m, 6-H), 5.50 (1 H, d, J 10,8-H), 5.76 (1 H, d, J 10, 7-H), 6.57 and 6.67 (2 H, ABq, 1 and 2-H), 7.41 (2 H, d, J 8, 21 and 23-H), 8.02 (2 H, d, J 8, 20 and 24-H); δ_C 20.63, 35.30, 40.59, 42.62, 43.01, (NMe), 46.70, 56.74 (OMe), 59.12, 68.68, 87.93, 114.35, 119.31, 126.95, 128.49, 128.60, 128.81, 129.75, 130.73, 131.33, 139.47, 142.18, 146.18, 146.52, 165.20; m/z 439 and 437 (M^+, 23 and 63%) 302(8), 300(24), 282(58), 229(26), 155(12), 141(33), 139(100), 111(38), 94(9), 59(44), 42(54).

(Found M^+, 439.1364 and 437.1394. $C_{25}H_{24}NClO_4$ requires 439.1383 and 437.1397).

Preparation of 6a-(4-Bromobenzoyloxy)-7,8-didehydro-4,5a-epoxy-3-methoxy-17-methyl-morphinan (6 X=Br in Figure 1)

To a solution of codeine (300 mg, 1 mmol) in pyridine (3 cm^3), under nitrogen, was added p-bromobenzoyl chloride (1.1 g, 5 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 10 minutes. $CHCl_3$ was added and the solution washed successively with dilute HCl/water/bicarbonate/water, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 5% MeOH in $CHCl_3$) to give the ester **(6 X=Br in Figure 1)** (441 mg, 92%). Recrystallisation from DCM-petroleum ether gave crystals m.p. 177-80°C; $\nu_{max}(CHCl_3)/cm^{-1}$ 1719 (C=O ester); $\delta_H(CDCl_3)$ 1.90 (1H, d, J 12.5, 15e-H), 2.11 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.37 (2 H, m, 10α and 16-H), 2.48 (3 H, s, NMe), 2.65 (1 H, dd, J 12.5, 4, 16-H), 2.85 (1 H, t, J 2.5, 14-H), 3.07 (1 H, d, J 18.5, 10β-H), 3.44 (1 H, q, J 3, 9-H), 3.72 (3 H, s, OMe), 5.19 (1 H, d, J 6.5, 5-H), 5.42 (1 H, m, 6-H), 5.51 (1 H, d, J 10, 8-H), 5.76 (1 H, d, J 10, 7-H), 6.57 and 6.67 (2 H, ABq, 1 and 2-H), 7.58 (2 H, d, J 8, 21 and 23-H), 7.94 (2 H, d, J 8, 20 and 24-H); δ_C 20.46, 35.14, 40.38, 42.54, 42.88 (NMe), 46.68, 56.74 (OMe), 59.10, 68.62, 87.84, 114.38, 119.34, 126.72, 128.16, 128.42, 128.92, 129.60, 130.63, 131.46, 131.60, 142.23, 146.66, 165.31; m/z 483 and 481 (M^+, 80 and 90%), 282(100), 346 and 344(25 and 27), 229(42), 185 and 183(76 and 83), 157(27), 105(34), 81(38), 59(52).

(Found M^+, 483.0887 and 481.0716. $C_{25}H_{24}NBrO_4$ requires 483.0869 and 481.0889).

Preparation of 7,8-Didehydro-4,5a-epoxy-3-methoxy-17-methyl-6a-(4-nitrobenzoyloxy)-morphinan (7 X=NO_2 in Figure 1)

To a solution of codeine (300 mg, 1 mmol) in pyridine (3 cm^3), under nitrogen was added p-nitrobenzoyl chloride (560 mg, 3 mmol) and the reaction stirred at room temperature for 4 hours. EtOAc was added and the solution washed with 5% $CuSO_4$ solution/water, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 15% MeOH in $CHCl_3$) and TLC plates (run in $CHCl_3$/MeOH/NH_4OH) to give the ester **(7 X=NO_2 in Figure 1)** (283 mg, 63%). Recrystallisation from DCM-petroleum ether gave crystals m.p. 186-87°C; $\nu_{max}(CHCl_3)/cm^{-1}$ 1722 (C=O ester); $\delta_H(CDCl_3)$ 1.90 (1 H, d, J 12.5, 15e-H), 2.08 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.34 (2 H, m, 10α and 16-H), 2.46 (3 H, s, NMe), 2.61 (1 H, dd, J 12, 4, 16-H), 2.83 (1 H, t, J 2.5, 14-H), 3.07 (1 H, d, J 18.5, 10β-H), 3.40 (1 H, q, J 3, 9-H), 3.71 (3 H, s, OMe), 5.20 (1 H, d, J 6.5, 5-H), 5.47 (1 H, m, 6-H), 5.55 (1 H, d, J 10, 8-H), 5.76 (1 H, d, J 10, 7-H), 6.58 and 6.67 (2 H, ABq, 1 and 2-H), 8.27 (4 H, m, 20, 21, 23 and 24-H); δ 20.30, 35.35, 40.66, 42.59, 43.09, (NMe), 46.74, 56.49 (OMe), 59.13, 69.17, 87.57, 113.86, 119.46, 123.40, 127.03, 127.80, 130.20, 130.60, 131.07, 142.18, 146.44, 150.59, 164.22; m/z 448 (M^+, 84%), 311(20), 282(82), 229(25), 152(16), 104(44), 92(20), 76(42), 59(39), 50(100), 44(58).
(Found M^+, 448.1607$C_{25}H_{24}N_2O_6$ requires 448.1634).

Preparation of 7,8-Didehydro-4,5a-epoxy-3-methoxy-6a-(4-methoxybenzoyloxy)-17-methyl-morphinan (8 X=OMe in Figure 1)

To a solution of codeine (300 mg, 1 mmol) in pyridine (3 cm^3), under nitrogen, was added p-anisoyl chloride (0.45 ml, 513 mg, 3 mmol) and the reaction stirred at room temperature for 10 minutes. EtOAc was added and the solution washed successively with dilute HCl/water/bicarbonate/water, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 5% MeOH in DCM) to give the ester **(8 X=OMe in Figure 1)** (426 mg, 98%). Recrystallisation from DCM-petroleum ether gave crystals m.p. 174-76°C; $\nu_{max}(CHCl_3)/cm^{-1}$ 1711 (C=O ester); $\delta_H(CDCl_3)$ 1.90 (1 H, d, J 12.5, 15e-H), 2.09 (1 H, dt, J 12, 5, 5, 15a-H), 2.36 (2 H, m, 10α and 16-H), 2.48 (3 H, s, NMe), 2.62 (1 H, dd, J 12, 4, 16-H), 2.83 (1 H, t, J 2.5,

14-H), 3.06 (1 H, d, J 18.5, 10β-H), 3.42 (1 H, q, J 3, 9-H), 3.44 (3 H, s, OMe), 3.74 (3 H, s, OMe), 5.18 (1 H, d, J 6.5, 5-H), 5.41 (1 H, m, 6-H), 5.48 (1 H, d, J 10, 8-H), 5.76 (1 H, d, J 10, 7-H), 6.55 and 6.66 (2 H, ABq, 1 and 2-H), 6.92 (2 H, d, J 9, 21 and 23-H), 8.04 (2 H, d, J 9, 20 and 24-H), δ_C 20.49, 35.28, 40.54, 42.69, 42.94 (NMe), 46.63, 55.42 (OMe), 57.02 (OMe), 59.05, 68.34, 88.32, 114.82, 119.19, 122.41, 126.97, 128.85, 129.42, 130.90, 131.98, 142.16, 146.78, 163.47, 165.77; m/z 433 (M^+, 43%), 282(20), 229(12), 152(14), 135(100), 77(16), 44(11).

(Found M^+, 433.1915 $C_{26}H_{27}NO_5$ requires 433.1889).

Preparation of 7,8-Didehydro-4,5a-epoxy-3-methoxy-6a-(3,4-methylenedioxybenzoyloxy)-17-methyl-morphinan (9)

To a solution of codeine (200 mg, 0.67 mmol) in DCM (2 cm^3) at 0°C, under nitrogen, was added piperonylic acid (333 mg, 2 mmol) and DMAP (82 mg, 0.67 mmol) and the solution was stirred for 30 min. DCC (152 mg, 0.74 mmol) was added and the reaction flask fitted with a calcium chloride guard tube. After stirring for 5 minutes at 0°C, the reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction mixture was filtered, washed with water/bicarbonate, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 10% MeOH in $CHCl_3$) to give the ester **(9)** (195 mg, 65%). Recrystallisation from DCM-petroleum ether gave crystals m.p. 63-5°C; $\nu_{max}(CHCl_3)/cm^{-1}$ 1711 (C=O ester); $\delta_H(CDCl_3)$ 1.90 (1 H, d, J 12.5, 15e-H), 2.11 (1 H, dt, J 12, 5, 5, 15a-H), 2.37 (2 H, m, 10α and 16-H), 2.46 (3 H, s, NMe), 2.64 (1 H, dd, J 12, 4, 16-H), 2.84 (1 H, t, J 2.5, 14-H), 3.06 (1 H, d, J 18.5, 10β-H), 3.44 (1 H, q, J 3, 9-H), 3.76 (3 H, s, OMe), 5.17 (1 H, d, J 6.5, 5-H), 5.41 (1 H, m, 6-H), 5.50 (1 H, d, J 10,8-H), 5.75 (1 H, d, J 10, 7-H), 6.03, (1 H, s, CH_2), 6.56 and 6.67 (2 H, ABq, 1 and 2-H), 6.84 (1 H, d, J 8, 23-H), 7.52 (1 H, d, J 1.5, 20-H), 7.70 (1 H, dd, J 8, 1.5, 24-H); m/z 447 (M^+, 40%) 310(17), 282(25), 229(13), 165(29), 149(100), 121(20), 91(8), 65(25), 42(21). (Found M^+, 447.1679. $C_{26}H_{25}NO_6$ requires 447.1682).

Preparation of 6a-(4-t-Butyldimethylsilyloxybenzoyloxy)-7,8-didehydro-4,5a-epoxy-3-methoxy-17-methyl-morphinan (10)

Freshly prepared p-t-BDMS-oxy benzoic acid (500 mg, 1.98 mmol) in DCM (5 cm^3),under nitrogen, was treated with oxalyl chloride (630 mg, 0.43 cm^3, 5 mmol). Effervescence implied formation of the acid chloride. On completion of the reaction, after 20 minutes, benzene (5 cm^3) was added and all solvents removed under reduced pressure. To the acid chloride residue, under nitrogen, was added a solution of codeine (200 mg, 0.67 mmol) in pyridine (3 cm^3) and the reaction stirred at room temperature for 2 hours. EtOAc was added and the solution washed with dilute HCl/water/bicarbonate/water, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 5% MeOH in DCM) to give the ester (**10**) (293 mg, 82%). Recrystallisation from DCM-petroleum ether gave crystals m.p. 102-5°C; ν_{max}(nujol)/cm^{-1} 1709 (C=O ester); δ_H($CDCl_3$) 0.22 (6 H, s, $SiMe_2$), 0.98 (9 H, s, $SiCMe_3$), 1.93 (1 H, d, J 12.5, 15e-H), 2.21 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.47 (2 H, m, 10α and 16-H), 2.56 (3 H, s, NMe), 2.83 (1 H, dd, J 12, 4, 16-H), 2.99 (1 H, t, J 2.5, 14-H), 3.08 (1 H, d, J 18.5, 10β-H), 3.60 (1 H, q, J 3, 9-H), 3.73 (3 H, s, OMe), 5.20 (1 H, d, J 6, 5-H), 5.41 (1 H, m, 6-H), 5.48 (1 H, d, J 10, 8-H), 5.78 (1 H, d, J 10, 7-H), 6.57 and 6.68 (2 H, ABq, 1 and 2-H), 6.86 (2 H, d, J 8.5, 21 and 23-H), 7.98 (2 H, d, J 8.5, 20 and 24-H); m/z 533 (M^+, 77%) 396(25), 282(57), 235(100), 229(25), 195(52), 149(14), 121(44), 91(14), 73(59), 59(18), 42(34).
(Found M^+, 533.2579. $C_{31}H_{39}NO_5Si$ requires 533.2597).

Preparation of 7,8-Didehydro-4,5a-epoxy-6a-(4-hydroxybenzoyloxy)-3-methoxy-17-methyl-morphinan (11)

To a solution of the codeine ester **10** (100 mg, 0.19 mmol) in THF, under nitrogen, at 0°C was added TBAF-1 M solution in THF (1 cm^3). After stirring for 5 minutes the reaction was allowed to warm up to room temperature and stirred for a further 2 hours. EtOAc was added and the solution washed several times with water, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 10% MeOH in $CHCl_3$) to give the ester (**11**) (48 mg, 61%). Recrystallisation from DCM-petroleum ether gave crystals m.p. 132-5°C;

ν_{max}(nujol)/cm^{-1} 3563 (OH). 1712 (C=O ester); δ_H($CDCl_3$) 1.91 (1 H, d, J 12.5, 15e-H), 2.15 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.41 (2 H, 10α and 16-H), 2.51 (3 H, s, NMe), 2.68 (1 H, m, 16-H), 2.89 (1 H, t, J 2.5, 14-H), 3.06 (1 H, d, J 18.5, 10β-H), 3.47 (1 H, q, J 3, 9-H), 3.73 (3 H, s, Ome), 5.19 (1 H, d, J 6, 5-H), 5.39 (1 H, m, 6-H), 5.47 (1 H, d, J 10, 8-H), 5.78 (1 H, d, J 10, 7-H), 6.56 and 6.67 (2 H, ABq, 1 and 2-H), 6.83 (2 H, d, J 9, 21 and 23-H), 7.95 (2 H, d, J 9, 20 and 24-H); m/z 419 (M^+, 20%) 282(19), 229(7), 162(40), 138(32), 121(80), 94(36), 73(32), 65(30), 44(100).

(Found M^+, 419.1749. $C_{25}H_{25}NO_5$ requires 419.1733).

EXAMPLE 2: SYNTHESIS OF MORPHINE ANALOGUES OF M6G

The synthesis of the compounds described in this Example is shown schematically in Figure 2

Preparation of 3-t-Butyldimethylsilyloxy-7,8-didehydro-4,5a-epoxy-17-methyl-morphinan-6-ol (1)

To a solution of morphine (2 g, 7 mmol), in THF, under nitrogen, was added NaH-60% dispersion in mineral oil (310 mg, 7.75 mmol) and the reaction stirred for 1 hour. tert-Butyldimethylsilyl chloride (1.27 g, 8.45 mmol) was added and the reaction stirred overnight. The mixture was filtered and THF removed under reduced pressure. The residue was purified by column chromatography (elution with 15% MeOH in $CHCl_3$). A cream powder was obtained (1.445 g, 52%) m.p. 121-22°C (lit. 122-123°C); ν_{max}(nujol)/cm^{-1} 3552 (OH), 1629; δ_H ($CDCl_3$) 0.16 (3 H, s, SiMe), 0.20 (3 H, s, SiMe), 0.98 (9 H, s, $SiCMe_3$), 1.89 (1 H, d, J 12, 15e-H), 2.21 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.43 (2 H, m, 10α and 16-H), 2.55 (3 H, s, NMe), 2.75 (1 H, dd, J 12.5, 4, 16-H), 2.89 (1 H, t, J 2.5, 14-H), 3.04 (1 H, d, J 18.5, 10β-H), 3.50 (1 H, q, J 3.5, 9-H), 4.19 (1 H, m, 6-H), 4.87 (1 H, d, J 6.5, 5-H), 5.26 (1 H, d, J 10, 8-H), 5.70 (1 H, d, J 10, 7-H), 6.50 and 6.60 (2 H, ABq, 1 and 2-H); m/z 503 (M^+, 15%) 446(10), 324(6), 266(9), 122(8), 105(100), 77(27), 57(16), 41(35). (Found M^+, 503.2446. $C_{30}H_{37}NO_4Si$ requires 503.2492).

Preparation of 6a-Benzoyloxy-3-t-butyldimethylsilyloxy-7,8-didehydro-4,5a-epoxy-17-methyl-morphinan (2 X=H in the relevant part of Figure 2)

To a solution of 3-t-BDMS-morphine (1) (300 mg, 0.75 mmol) in pyridine (3 cm^3) with a little DMAP, under nitrogen, was added benzoyl chloride (0.5 cm^3, 317 mg, 2.25 mmol) and the reaction stirred at room temperature for 10 minutes. $CHCl_3$ was added and the solution washed successively with 5% $CuSO_4$ solution/water, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 3% MeOH) in CH_2Cl_2) to give the ester **(2 X=H in Figure 2)** (336 mg, 89%) m.p. 133-5°C; $\nu_{max}(CHCl_3)/cm^{-1}$ 1717 (C=O); δ_H ($CDCl_3$) 0.13 (6 H, s, $SiMe_2$), 0.84 (9 H, s, $SiCMe_3$), 1.93 (1 H, d, J 11, 15e-H), 2.33 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.56 (2 H, m, 10α and 16-H), 2.64 (3 H, s, NMe), 2.95 (1 H, dd, J 12.5, 4, 16-H), 3.09 (2 H, m, 10β and 14-H), 3.71 (1 H, q, J 3.5, 9-H), 5.24 (1 H, d, J 6, 5-H), 5.44 (2 H, m, 6 and 8-H), 5.79 (1 H, d, J 10, 7-H), 6.51 and 6.62 (2 H, ABq, 1 and 2-H), 7.42 (2 H, t, J 7.5 21 and 23-H), 7.56 (1 H, t, J 7.5, 22-H), 8.09 (2H, d, J 7, 20 and 24-H).

Preparation of 3-t-Butyldimethylsilyloxy-7,8-didehydro-4,5a-epoxy-6a-(4-fluoro-benzoyloxy)-17-methyl-morphinan (3 X=F in the relevant part of Figure 2)

To a solution of 3-t-BDMS-morphine (1) (300 mg, 0.75 mmol) in pyridine (3 cm^3), under nitrogen, was added p-fluorobenzoyl chloride (0.3 cm^3, 360 mg, 2.25 mmol) and the reaction stirred at room temperature for 20 minutes. $CHCl_3$ was added and the solution washed successively with 5% $CuSO_4$ solution/water, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 3% MeOH in CH_2Cl_2) to give the ester **(3 X=F)** (342 mg, 87%) m.p. 134-6°C; $\nu_{max}(CHCl_3)/cm^{-1}$ 1717 (C=O ester); δ_H ($CDCl_3$) 0.04 (6 H, s, $SiMe_2$), 0.84 (9 H, s, $SiCMe_3$), 1.90 (1 H, d, J 11, 15e-H), 2.24 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.52 (2 H, m, 10α and 16-H), 2.58 (3 H, s, NMe), 2.85 (1 H, dd, J 12.5, 4, 16-H), 3.01 (1 H, t, J 2.5, 14-H), 3.08 (1 H, d, J 18.5 10β-H), 3.66 (1 H, q, J 3, 9-H), 5.19 (1 H, d, J 6.5, 5-H), 5.39 (1 H, m, 6-H), 5.48 (1 H, d, J 10, 8-H), 5.76 (1 H, d, J 10, 7-H), 6.50 and 6.61 (2 H, ABq, 1 and 2-H), 7.07 and 7.11 (2 x 1 H, d, J 8.5, 21 and 23-H), 8.08 and 8.12 (2 x 1 H, d, J 8.5, 20 and 24-H); δ_C -4.85, 18.06, 21.11, 25.51, 34.56, 39.55, 42.16 (NMe), 42.71, 46.39, 58.90, 69.16, 87.79, 115.24, 115.59, 119.31, 121.71, 126.11, 128.80, 129.04, 130.11, 131.96,

132.52, 132.52, 132.67, 137.76, 149.03, 163.86, 168.86, 168.12; m/z 521 (M^+, 14%) 464(9), 382(5), 324(4), 284(5), 140(20), 123(100), 95(28), 73(21), 59(9), 42(11). (Found M^+, 521.2413. $C_{30}H_{36}NFO_4Si$ requires 521.2398).

Preparation of 3-t-Butyldimethylsilyloxy-6a-(4-chlorobenzoyloxy)-7,8-didehydro-4,5a-epoxy-17-methyl-morphinan (4 X=Cl in the relevant part of Figure 2)

To a solution of 3-t-BDMS-morphine **(1)** (300 mg, 0.75 mmol) in pyridine (3 cm^3), under nitrogen, was added p-chlorobenzoyl chloride (0.3 cm^3, 396 mg, 2.25 mmol) and the reaction stirred at room temperature for 5 minutes. $CHCl_3$ was added and the solution washed successively with 5% $CuSO_4$ solution/water, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 3% MeOH in CH_2Cl_2) to give the ester **(4 X=Cl)** (381 mg, 94%) m.p. 119-21°C; $\nu_{max}(CHCl_3)/cm^{-1}$ 1719 (C=O ester); $\delta_H(CDCl_3)$ 0.05 (6 H, s, $SiMe_2$), 0.85 (9 H, s, $SiCMe_3$), 1.84 (1 H, d, J 11, 15e-H), 2.05 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.34 (2 H, m, 10α and 16-H), 2.45 (3 H, s, NMe), 2.57 (1 H, dd, J 12.5, 4, 16-H), 2.77 (1 H, t, J 2.5, 14-H), 3.04 (1 H, d, J 18.5, 10β-H), 3.38 (1 H, q, J 3.5, 9-H), 5.16 (1 H, d, J 6.5 5-H), 5.39 (1 H, m, 6-H), 5.48 (1 H, d, J 10, 8-H), 5.72 (1 H, d, J 10, 7-H), 6.47 and 6.58 (2 H, ABq, 1 and 2-H), 7.41 (2 H, d, J 8.5, 21 and 23-H), 8.01 (2 H, d, J 8.5, 20 and 24-H), δ_C -4.78, 18.31. 21.46, 25.03, 32.76, 37.64, 40.86 (NMe), 41.56, 46.50, 59.50, 68.39, 86.77, 119.47, 122.11, 127.01, 128.08, 128.38, 129.29, 130.89, 131.11, 137.76, 139.45, 148.03, 164.76; m/z 539 and 537 (M^+, 23 and 55%) 482(13), 480(34), 456(15), 413(13), 382(25), 324(18), 300(14), 266(14), 141(35), 139(91), 123(7), 94(10), 73(100), 59(36), 42(48).
(Found M^+, 539.2070 and 537.2123. $C_{30}H_{36}NClO_4Si$ requires 539.2072 and 537.2102).

Preparation of 6a-(4-Bromobenzoyloxy)-3-t-butyldimethylsilyoxy-7,8-didehydro-4,5a-epoxy-17-methyl-morphinan (5 X=Br in the relevant part of Figure 2)

To a solution of 3-t-BDMS-morphine **(1)** (300 mg, 0.75 mmol) in pyridine (3 cm^3) with a little DMAP, under nitrogen, was added p-bromobenzoyl chloride (825 mg, 3.75 mmol) and the reaction stirred at room temperature for 20 minutes. $CHCl_3$ was added and the solution washed successively with 5% $CuSO_4$ solution/water, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by column

chromatography (elution with 3% MeOH in CH_2Cl_2) to give the ester **(5 X=Br)** (315 mg, 72%) m.p. 137-8°C; $\nu_{max}(CHCl_3)/cm^{-1}$ 1719 (C=O ester); δ_H ($CDCl_3$) 0.01 (3 H, s, SiMe), 0.04 (3 H, s, SiMe), 0.84 (9 H, s, $SiCMe_3$), 1.87 (1 H, d, J 11, 15e-H), 2.15 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.40 (2 H, m, 10α and 16-H), 2.47 (3 H, s, NMe), 2.72 (1 H, dd, J 12, 4, 16-H), 2.88 (1 H, t, J 2.5, 14-H), 3.06 (1 H, d, J 18.5, 10β-H), 3.50 (1 H, q, J 3, 9-H), 5.17 (1 H, d, J 6.5, 5-H), 5.38 (1 H, m, 6-H), 5.48 (1 H, d, J 10, 8-H), 5.73 (1 H, d, J 10, 7-H), 6.49 and 6.59 (2 H, ABq, 1 and 2-H), 7.56 (2 H, d, J 8.5, 21 and 23-H), 7.95 (2 H, d, J 8.5, 20 and 24-H); m/z 583 and 581 (M^+, 22 and 22%) 527(15), 525(14), 382(19), 266(15), 202(29), 200(30), 185(96), 183(100), 155(31), 123(41), 105(33), 75(50), 73(62), 51(56), 41(58).

(Found M^+, 583.1641 and 581.1603. $C_{30}H_{36}NBrO_4Si$ requires 583.1578 and 581.1597).

Preparation of 3-t-Butyldimethylsilyloxy-7,8-didehydro-4,5a-epoxy-17-methyl-6a-(4-nitrobenzoyloxy)-morphinan (6 X=NO_2 in the relevant part of Figure 2)

To a solution of 3-t-BDMS-morphine **(1)** (150 mg, 0.37 mmol) in pyridine (5 cm^3) with a little DMAP, under nitrogen, was added p-nitrobenzoyl chloride (210 mg, 1.13 mmol) and the reaction stirred overnight. EtOAc was added and the solution washed with 5% $CuSO_4$ solution/water, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 10% MeOH in $CHCl_3$) to give the ester **(6 X=NO_2)** (162 mg, 78%) m.p. 129-31°C; ν_{max}(nujol)/cm^{-1} 1718 (C=O ester); δ_H ($CDCl_3$) 0.03 (3 H, s, SiMe), 0.06 (3 H, s, SiMe), 0.85 (9 H, s, $SiCMe_3$), 1.89 (1 H, d, J 11, 15e-H), 2.13 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.40 (2 H, m, 10α and 16-H), 2.50 (3 H, s, NMe), 2.65 (1 H, dd, J 12.5, 4, 16-H), 2.85 (1 H, t, J 2.5, 14-H), 3.10 (1 H, d, J 18.5, 10β-H), 3.44 (1 H, q, J 3, 9-H), 5.20 (1 H, d, J 6.5, 5-H), 5.43 (1 H, m, 6-H), 5.54 (1 H, d, J 10, 8-H), 5.75 (1 H, d, J 10, 7-H), 6.49 and 6.59 (2 H, ABq, 1 and 2-H), 8.29 (4 H, s, 20, 21, 23 and 24-H); δ_C -4.92, 17.96, 20.36, 25.35, 35.43, 40.71, 42.87, 42.95 (NMe), 46.51, 58.91, 69.85, 87.37, 119.19, 121.23, 123.29, 127.27, 127.49, 130.27, 130.43, 131.01, 135.29, 137.06, 148.42, 150.48, 163.98; m/z 548 (M^+, 52%) 491(38), 382(25), 266(21), 137(18), 122(14), 104(40), 92(20), 77(45), 50(79), 41(100).

(Found M^+, 548.2331. $C_{30}H_{36}N_2O_6Si$ requires 548.2342).

Preparation of 3-t-Butyldimethylsilyloxy-7,8-didehydro-4,5a-epoxy-6a-(4-methoxy-benz yloxy)-17-methyl-morphinan (7 X=ome in the relevant part f Figure 2)

To a solution of 3-t-BDMS-morphine **(1)** (100 mg, 0.25 mmol) in pyridine (3 cm^3), under nitrogen, was added p-anisoyl chloride (0.1 cm^3, 128 mg, 0.75 mmol) and the reaction stirred at room temperature for 30 minutes. EtOAc was added and the solution washed successively with dilute HCl/water/bicarbonate/water, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 5% MeOH in $CHCl_3$) to give the ester **(7 X=ome)** (82 mg, 61%) m.p. 173-5°C; $\nu_{max}(CHCl_3)/cm^{-1}$ 1710 (C=O ester); $\delta_H(CDCl_3)$ 0.04 (3 H, s, SiMe), 0.06 (3 H, s, SiMe), 0.87 (9 H, s, $SiCMe_3$), 1.88 (1 H, d, J 11, 15e-H), 2.10 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.38 (2 H, m, 10α and 16-H), 2.46 (3 H, s, NMe), 2.61 (1 H, dd, J 12.5, 4, 16-H), 2.80 (1 H, t, J 2.5, 14-H), 3.05 (1 H, d, J 18.5, 10β-H), 3.40 (1 H, q, J 3, 9-H), 3.87 (1H, s, O-Me), 5.17 (1 H, d, J 6.5, 5-H), 5.38 (1 H, m, 6-H), 5.45 (1 H, d, J 10, 8-H), 5.73 (1 H, d, J 10, 7-H), 6.47 and 6.59 (2 H, ABq, 1 and 2-H), 6.90 (2 H, d, J 9, 21 and 23-H), 8.06 (2 H, d, J 9, 20 and 24-H); m/z 533 (M^+, 8%) 476(4), 382(3), 324(4), 296(4), 152(5), 135(100), 92(4), 73(11), 51(9), 41(10).
(Found M^+, 533.2602. $C_{31}H_{39}NO_5Si$ requires 533.2598).

Preparation of 3-t-Butyldimethylsilyloxy-6a-(4-t-butyldimethylsilyloxybenzoyloxy)-7,8-didehydro-4,5a-epoxy-17-methyl-morphinan (8 V=OTBDMS in the relevant part of Figure 2)

Freshly prepared p-t-BDMS-oxy benzoic acid (500 mg, 1.98 mmol) in DCM (5 cm^3), under nitrogen, was treated with oxalyl chloride (630 mg, 0.43 cm^3, 5 mmol). Effervescence implied formation of the acid chloride. On completion of the reaction, after 20 minutes, benzene (5 cm^3) was added and all solvents removed under reduced pressure. To the acid chloride residue, under nitrogen, was added a solution of 3-t-BDMS-morphine **(1)** (250 mg, 0.63 mmol) in pyridine (3 cm^3) and the reaction stirred at room temperature overnight. EtOAc was added and the solution washed with dilute HCl/water/bicarbonate/water, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 5% MeOH in DCM) to give the ester **(8 X=OTBDMS)** (276 mg, 70%) m.p. 122-4°C; δ_H ($CDCl_3$) 0.02 (3 H,

s, SiMe), 0.04 (3 H, s, SiMe), 0.17 (6 H, s, $SiMe_2$) 0.82 (9 H, s, $SiCMe_3$), 0.94 (9 H, s, $SiCMe_3$), 1.83 (1 H, d, J 11, 15e-H), 2.07 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.34 (2 H, m, 10α and 16-H), 2.42 (3 H, s, NMe), 2.58 (1 H, dd, J 12, 4, 16-H), 2.78 (1 H, t, J 2.5, 14-H), 3.00 (1 H, d, J 18.5, 10β-H), 3.39 (1 H, q, J 3, 9-H), 5.13 (1 H, d, J 6.5, 5-H), 5.31 (1 H, m, 6-H), 5.40 (1 H, d, J 10, 8-H), 5.68 (1 H, d, J 10, 7-H), 6.42 and 6.53 (2 H, ABq, 1 and 2-H), 6.80 (2 H, d, J 9, 21 and 23-H), 7.94 (2 H, d, J 9, 20 and 24-H).

Preparation of 3-t-Butyldimethylsilyloxy-7,8-didehydro-4,5a-epoxy-17-methyl-6a-succinyloxy-morphinan (9)

A mixture of 3-t-BDMS-morphine **(1)** (300 mg, 0.75 mmol) and succinic anhydride (375 mg, 3.75 mmol) in pyridine (5 cm^3), under nitrogen, was refluxed for 1 hour. The hot reaction mixture was poured onto ice and the resulting white precipitate collected on a filter. The precipitate was washed with cold water. Crystallisation from DCM-petroleum ether gave the ester **(9)** (225 mg, 60%) m.p. 144-7°C; $\nu_{max}(CHCl_3)/cm^{-1}$ 1735 (C=O ester), 1604 (C=O acid); δ_H ($CDCl_3$) 0.15 (3 H, s, SiMe), 0.20 (3 H, s, SiMe), 0.98 (9 H, s, $SiCMe_3$), 1.86 (1 H, d, J 12, 15e-H), 2.41-2.82 (10 H, m, N-Me, 2xCH_2, 10a, 15α and 16-H), 3.00 (1 H, d, J 18.5, 10β-H), 3.10 (2 H, m, 14 and 16-H), 3.79 (1 H, q, J 3.5, 9-H), 5.09 (1 H, d, J 6, 5-H), 5.28 (2 H, m, 6 and 8-H), 5.56 (1 H, d, J 10, 7-H), 6.47 and 6.61 (2 H, ABq, 1 and 2-H); δ_C -4.78, -4.55, 18.15, 21.19, 25.66, 30.18, 30.95, 33.20, 37.63, 40.92 (NMe), 42.01, 46.16, 58.66, 68.08, 88.18, 119.19, 122.01, 124.45, 127.71, 129.60, 129.94, 137.80, 148.62, 172.70, 172.85; m/z 499 (M^+, 3%) 456(5), 382(9), 324(11), 267(12), 215(29), 105(24), 73(100), 41(94).
(Found M^+, 499.2388. $C_{27}H_{37}NO_6Si$ requires 499.2390).

Preparation of 3-t-Butyldimethylsilyloxy-6a-(2-carboxybenzoyloxy)-7,8-didehydro-4,5a-epoxy-17-methyl-morphinan (10)

A mixture of 3-t-BDMS-morphine **(1)** (250 mg, 0.63 mmol) and phthalic anhydride (500 mg, 3.38 mmol) in pyridine (2 cm^3), under nitrogen, was refluxed for 1 hour. The hot reaction mixture was poured onto ice and the resulting white precipitate collected on a filter. The precipitate was washed with cold water. Crystallisation from DCM-petroleum ether gave the ester **(10)** (237 mg, 69%) m.p. 193-5°C (decomp); $\nu_{max}(CHCl_3)/cm^{-1}$

1714 (C=O ester), 1602 (C=O acid); δ_H ($CDCl_3$) 0.04 (3H, s, SiMe), 0.06 (3 H, s, SiMe), 0.88 (9 H, s, $SiCMe_3$), 1.97 (1 H, d, J 11, 15e-H), 2.78-2.88 (3 H, m, 10a, 15α and 16-H), 2.91 (3 H, s, NMe), 3.08 (1 H, d, J 18.5, 10β-H), 3.45 (1 H, dd, J 12, 4, 16-H), 3.59 (1 H, t, J 2.5, 14-H), 4.03 (1 H, q, J 3.5, 9-H), 5.32 (1 H, d, J 6.5, 5-H), 5.40 (1 H, d, J 10, 8-H), 5.55 (1 H, m, 6-H), 5.80 (1 H, d, J 10, 7-H), 6.54 and 6.66 (2 H, ABq, 1 and 2-H), 7.38 (1 H, t, J 7.5, 22-H), 7.52 (1 H, t, J 7.5, 23-H), 7.66 (1 H, d, J 7.5, 21-H), 7.92 (1 H, d, J 7.5, 24-H).

Preparation of 6a-Benzoyloxy-7,8-didehydro-4,5a-epoxy-17-methyl-morphinan-3-ol (11 X=H in the relevant parts of Figure 2)

To a solution of the ester **(2)** (150 mg, 0.27 mmol) in dry THF (3 cm^3), under nitrogen, at 0°C, was added TBAF (1 M solution in THF) (1 cm^3). The reaction was stirred at 0°C for 5 minutes and then allowed to warm up to room temperature, with stirring continuing overnight. The reaction mixture was dissolved in EtOAc and washed with water, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by TLC to give the ester **(11 X=H)**, a white powder, (102 mg, 88%). Crystallisation was from $CHCl_3$/MeOH. m.p. 264-8°C (decomp); (found C, 73.25; H, 5.85; N, 3.65. $C_{24}H_{23}NO_4$ requires C, 73.2; H, 5.95; N, 3.55%); ν_{max}(nujol)/cm^{-1} 1713 (C=O ester); δ_H(CD_3OD/$CDCl_3$) 1.88 (1 H, d, J 12.5, 15e-H), 2.08 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.37 (2 H, m, 10α and 16-H), 2.44 (3 H, s, NMe), 2.61 (1 H, dd, J 12.5, 4, 16-H), 2.80 (1 H, t, J 2.5, 14-H), 3.04 (1 H, d, J 18.5, 10β-H), 3.38 (1 H, q, J 3, 9-H), 5.21 (1 H, d, J 6.5, 5-H), 5.41 (1 H, m, 6-H), 5.49 (1 H, d, J 10, 8-H), 5.76 (1 H, d, J 10, 7-H), 6.52 and 6.63 (2 H, ABq, 1 and 2-H), 7.45 (2 H, t, J 8, 21 and 23-H), 7.59 (1 H, t, J 7.5, 22-H), 8.10 (2 H, d, J 7, 20 and 24-H); δ_C 20.30, 34.92, 40.23, 42.71 (NMe), 46.58, 58.98, 68.74, 88.07, 116.69, 119.63, 125.34, 128.16, 128.35, 129.46, 129.58, 129.71, 129.71, 129.92, 133.20, 138.27, 144.94, 166.24; m/z 389 (M^+, 38%) 268(33), 215(13), 146(12), 122(11), 105(100), 94(6), 77(34).
(Found M^+, 389.1623. $C_{24}H_{23}NO_4$ requires 389.1627).

Preparation of 7,8-Didehydro-4,5a-epoxy-6a-(4-fluorobenzoyloxy)-17-methyl-morphinan-3-ol (12 X=F in the relevant parts of Figure 2)

To a solution of the ester **(3)** (150 mg, 0.29 mmol) in dry THF (3 cm^3), under nitrogen, at 0°C, was added TBAF (1 M solution in THF) (1 cm^3). The reaction was stirred at 0°C for 5 minutes and then allowed to warm up to room temperature, with stirring continuing overnight. The reaction mixture was dissolved in EtOAc and washed with water, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by TLC to give the ester **(12 X=F)**, a white powder, (96 mg, 82%). Crystallisation was from $CHCl_3$/MeOH. m.p. 279-83°C (decomp); (Found: C, 70.45; H, 5.4; N, 3.3. $C_{24}H_{22}NFO_4$ requires C, 70.75; H, 5.45; N, 3.45%); ν_{max}(nujol)/cm^{-1} 1713 (C=O ester); δ_H(CD_3OD/$CDCl_3$) 1.88 (1 H, d, J 11, 15e-H), 2.06 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.37 (2 H, m, 10α and 16-H), 2.45 (3 H, s, NMe), 2.62 (1 H, dd, J 12.5, 4, 16-H), 2.80 (1 H, t, J 2.5, 14-H), 3.04 (1 H, d, J 18.5, 10β-H), 3.38 (1 H, q, J 3.5, 9-H), 5.18 (1 H, d, J 6.5, 5-H), 5.40 (1 H, m, 6-H), 5.50 (1 H, d, J 10,7-H), 6.51 and 6.62 (2 H, ABq, 1 and 2-H), 7.11 and 7.15 (2 x 1 H, d, J 8.5, 21 and 23-H), 8.09 and 8.11 (2 x 1 H, d, J 8.5, 20 and 24-H); δ_C 21.28, 34.77, 40.06, 42.59 (NMe), 46.56, 58.95, 68.66, 87.84, 115.21, 115.56, 116.64, 119.53, 125.15, 128.10, 129.39, 129.86, 132.26, 132.41, 138.36, 145.03, 163.80, 165.32, 167.84; m/z 407 (M^+, 30%) 284(17), 268(33), 215(14), 146(13), 123(100), 95(31), 84(21). (Found M^+, 407.1593. $C_{24}H_{22}NFO_4$ requires 407.1533).

Preparation of 6a-(4-Chlorobenzoyloxy)-7,8-didehydro-4,5a-epoxy-17-methyl-morphinan-3-ol (13 X=Cl in the relevant parts of Figure 2)

To a solution of the ester **(4)** (150 mg, 0.28 mmol) in dry THF (3 cm^3), under nitrogen, at 0°C, was added TBAF (1 M solution in THF) (1 cm^3). The reaction was stirred at 0°C for 5 minutes then allowed to warm up to room temperature, with stirring continuing overnight. The reaction mixture was dissolved in EtOAc and washed with water, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by TLC to give the ester **(13 X-Cl)** 105 mg, 89%). Crystallisation was from $CHCl_3$/MeOH. m.p. 269-72°C (decomp); (Found: C, 67.7; H, 5.2; N, 3.25. $C_{24}H_{22}NClO_4$ requires C, 68.0; H, 5.25; N, 3.3%); ν_{max}(nujol)/cm^{-1} 1719 (C=O ester); δ_H(CD_3OD/$CDCl_3$) 1.95 (1 H, d, J 12, 15e-H), 2.29 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.57 (2 H, m, 10α and 16-H),

2.66 (3 H, s, NMe), 3.04 (3 H, m, 10β, 14 and 16-H), 3.75 (1 H, q, J 3, 9-H), 5.22 (1 H, d, J 6.5, 5-H), 5.41 (1 H, m, 6-H), 5.51 (1 H, d, J 10, 8-H), 5.79 (1 H, d, J 10, 7-H), 6.55 and 6.65 (2 H, ABq, 1 and 2-H), 7.39 and 7.42 (2 x 1 H, d, J 8.5, 21 and 23-H), 7.98 and 8.01 (2 x 1 H, d, J 8.5, 20 and 24-H); m/z 423 and 425 (M^+, 36 and 12%) 300(8), 268(54), 215(21), 141(34), 139(100), 111(32), 94(10), 81(17).

(Found M^+, 425.1207 and 423.1237. $C_{24}H_{22}NClO_4$ requires 425.1227 and 423.1268).

Preparation of 6a-(4-Bromobenzoyloxy)-7,8-didehydro-4,5a-epoxy-17-methyl-morphinan-3-ol (14 X=Br in the relevant parts of Figure 2)

To a solution of the ester **(5)** (150 mg, 0.26 mmol) in dry THF (3 cm^3), under nitrogen, at 0°C, was added TBAF (1M solution in THF) (1 cm^3). The reaction was stirred at 0°C for 5 minutes and then allowed to warm up to room temperature, with stirring continuing overnight. The reaction mixture was dissolved in EtOAc and washed with water, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by TLC to give the ester **(14 X=Br)**, a white powder, (97 mg, 80%). Crystallisation was from $CHCl_3$/MeOH. m.p. 279-84°C (decomp); (Found: C, 61.25; H, 4.7; N, 3.05. $C_{24}H_{22}NBrO_4$ requires C, 61.5; H, 4.7; N, 3.0%); ν_{max}(nujol)/cm^{-1} 1718 (C=O ester); δ_H(CD_3OD/$CDCl_3$) 1.88 (1 H, d, J 12.5, 15e-H), 2.08 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.37 (2 H, m, 10α and 16-H), 2.46 (3 H, s, NMe), 2.62 (1 H, dd, J 12.5, 4, 16-H), 2.81 (1 H, t, J 2.5, 14-H), 3.04 (1 H, d, J 18.5, 10β,-H), 3.40 (1 H, q, J 3, 9-H), 5.18 (1 H, d, J 6.5, 5-H), 5.40 (1 H, m, 6-H), 5.51 (1 H, d, J 10, 8-H), 5.74 (1 H, d, J 10, 7-H), 6.51 and 6.63 (2 H, ABq, 1 and 2-H), 7.60 (2 H, d, J 8.5, 21 and 23-H), 7.95 (2 H, d, J 8.5, 20 and 24-H); m/z 469 and 467 (M^+, 39 and 42%) 268(95), 215(36), 185(92), 183(100), 155(42), 141(23), 94(17), 81(32).

(Found M^+, 469.0544 and 467.0583. $C_{24}H_{22}NBrO_4$ requires 469.0713 and 467.0733).

Preparation of 7,8-Didehydro-4,5a-epoxy-17-methyl-6a-(4-nitrobenzoyloxy)-morphinan-3-ol (15 X=NO_2 in the relevant parts of Figure 2)

To a solution of the ester **(6)** (300 mg, 0.18 mmol) in dry THF (5 cm^3), under nitrogen, at 0°C, was added TBAF (1 M solution in THF) (1 cm^3). The reaction was stirred at 0°C for 5 minutes and then allowed to warm up to room temperature, with stirring

continuing overnight. The reaction mixture was evaporated under reduced pressure. The crude product was purified by TLC to give the ester **(15 X=NO_2)**, a yellow powder, (206 mg, 87%). Crystallisation was from DMSO/H_2O. m.p. 260-9°C (decomp); (Found: C, 64.0; H, 5.4; N, 5.95. $C_{24}H_{22}N_2O_6$ requires C, 63.7; H, 5.35; N, 6.2%); ν_{max}(nujol)/cm^{-1} 1719 (C=O ester); δ_H(DMSO-d_6) 1.62 (1 H, d, J 11, 15e-H), 2.06 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.21 (2 H, m, 10α and 16-H), 2.31 (3 H, s, NMe), 2.48 (1 H, m, 16-H), 2.76 (1 H, t, J 2.5, 14-H), 2.89 (1 H, d, J 18.5, 10β-H), 3.31 (1 H, q, J 3, 9-H), 5.12 (1 H, d, J 6.5,5-H), 5.43 (1 H, m, 6-H), 5.55 (1 H, d, J 10, 8-H), 5.72 (1 H, d, J 10, 7-H), 6.41 and 6.47 (2 H, ABq, 1 and 2-H), 8.22 (2 H, d, J 9, 20 and 24-H), 8.36 (2 H, d, J 9, 21 and 23-H); δ_C 19.90, 34.85, 39.94, 42.12, 42.78 (NMe), 46.32, 58.27, 69.38, 86.84, 116.48, 119.16, 123.87, 125.18, 127.64, 130.46, 130.53, 130.98, 135.32, 138.88, 145.14, 150.36, 163.90; m/z 434 (M^+, 14%) 268(15), 248(16), 136(11), 104(17), 91(21), 88(19), 44(100). (Found M^+, 434.1479. $C_{24}H_{22}N_2O_6$ requires 434.1478).

Preparation of 7,8-Didehydro-4,5a-epoxy-6a-(4-hydroxybenzoyloxy)-17-methyl-morphinan-3-ol (16 X=OH in the relevant parts of Figure 2)

To a solution of the ester **(8)** (500 mg, 0.79 mmol) in dry THF (5 cm^3), under nitrogen, at 0°C, was added TBAF (1 M solution in THF) (2 cm^3). The reaction was stirred at 0°C for 5 minutes and then allowed to warm up to room temperature, with stirring continuing overnight. The reaction mixture was dissolved in EtOAc and washed with water, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by TLC to give the ester **(16 X=OH)** (268 mg, 84%). Crystallisation was from $CHCl_3$/MeOH. m.p. 178-82°C (decomp); (Found: C, 68.1; H, 5.65; N, 3.2. $C_{24}H_{23}NO_5$ requires C, 68.1; H, 5.9; N, 3.3%); ν_{max}(nujol)/cm^{-1} 1715 (C=O ester); δ_H(CD_3OD/$CDCl_3$) 1.81 (1 H, d, J 11.5, 15e-H), 2.05 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.34 (2 H, m, 10α and 16-H), 2.43 (3 H, s, NMe), 2.61 (1 H, dd, J 12.5, 4, 16-H), 2.79 (1 H, t, J 2.5, 14-H), 3.02 (1 H, d, J 18.5, 10β,-H), 3.38 (1 H, q, J 3, 9-H), 5.15 (1 H, d, J 6, 5-H), 5.34 (1 H, m, 6-H), 5.46 (1 H, d, J 10, 8-H), 5.73 (1 H, d, J 10, 7-H), 6.50 and 6.63 (2 H, ABq, 1 and 2-H), 6.85 (2 H, d, J 9, 21 and 23-H), 7.95 (2 H, d, J 9, 20 and 24-H); δ_C 20.38, 34.68, 39.94, 42.48 (NMe), 42.62, 46.56, 58.94, 68.27, 88.15, 115.30, 116.78, 119.58, 120.47, 125.27, 128.48, 129.19, 129.97, 132.04, 138.28, 145.02, 162.06, 166.27;

m/z 405 (M^+, 11%) 285(14), 210(14), 155(15), 138(23), 121(84), 94(100), 65(42), 51(28), 44(49). (Found M^+, 405.1569. $C_{24}H_{23}NO_5$ requires 405.1576).

Preparation of 7,8-didehydro-4,5a-epoxy-17-methyl-6a-succinyloxy-morphinan-3-ol (17)

To a solution of the ester **(9)** (150 mg, 0.3 mmol) in THF (2 cm^3), under nitrogen, at 0°C, was added TBAF (1 M solution in THF) (1 cm^3). The reaction was stirred at 0°C for 5 minutes and then allowed to warm up to room temperature, with stirring continuing overnight. The reaction mixture was quenched with water. The resulting precipitate was collected on a filter giving the acid/ester **(17)** (62 mg, 54%). Crystallisation was from $CHCl_3$/MeOH. m.p. 275-9°C (decomp); ν_{max}(nujol)/cm^{-1} 3382 (OH), 1736 (C=O ester), 1605 (C=O acid); δ_H(CD_3OD/$CDCl_3$) 1.96 (1 H, d, J 12, 15e-H), 2.43-2.86 (10 H, m, N-Me, 2xCH_2, 10α, 15a, and 16-H), 3.04 (1 H, d, J 18.5, 10β-H), 3.15 (2 H, m, 14 and 16-H), 3.83 (1 H, q, J 3.5, 9-H), 5.11 (1 H, d, J 6, 5-H), 5.30 (2 H, m, 6 and 8-H), 5.58 (1 H, d, J 10, 7-H), 6.57 and 6.61 (2 H, ABq, 1 and 2-H).

Preparation of 6a-(2-Carboxybenzoyloxy)-7,8-didehydro-4,5a-epoxy-17-methyl-morphinan-3-ol (18)

To a solution of the ester **(10)** (300 mg, 0.18 mmol) in pyridine (5 cm^3), under nitrogen, at 0°C, was added HF-pyridine (1 cm^3). The reaction was stirred at 0°C for 5 minutes and then allowed to warm up to room temperature, with stirring continuing overnight. The reaction mixture was quenched with water. The resulting precipitate was collected on a filter giving the acid/ester **(18)** (135 mg, 57%). Crystallisation was from $CHCl_3$/MeOH. m.p. 225-8°C (decomp); (Found: C, 65.5; H, 5.35; N, 2.85. $C_{25}H_{23}NO_6$ requires C, 65.2; H, 5.65; N, 3.05%); ν_{max}(nujol)/cm^{-1} 3398 (OH), 1716 (C=O ester), 1601 (C=O acid); δ_H(CD_3OD/$CDCl_3$) 2.03 (1 H, d, J 10, 15e-H), 2.90 (3 H, m, 10α, 15a and 16-H), 3.01 (3 H, s, NMe), 3.21 (1 H, d, J 18.5, 10β-H), 3.48 (1 H, d, J 8, 16-H), 3.86 (1 H, t, J 2.5, 14-H), 4.12 (1 H, q, J 3, 9-H), 5.53 (2 H, m, 6 and 8-H), 5.66 (1 H, d, J 6.5, 5-H), 5.91 (1 H, d, J 10, 7-H), 6.59 and 6.63 (2 H, ABq, 1 and 2-H), 7.40 (1 H, m, 22-H), 7.56 (2 H, m, 21 and 23-H), 7.92 (1 H, d, J 7.5, 23-H); m/z (M^+, 433) 285(100), 268(11), 215(21), 162(29), 124(17), 104(96), 76(79), 42(31).

IN VIVO EXPERIMENTS

EXAMPLE 3: OPIOID RECEPTOR PROFILE

Solutions

Tris buffer was prepared as 50mM in distilled water and the pH adjusted to 7.4 with HCl(4N). Tris-NaCl buffer contained 100mM NaCl.

Krebs buffer solution for the myenteric plexus longitudinal muscle (MPLM) comprised the following:-

NaCl (6.92g/1), KCl (0.35g/1), KH_2PO_4 (0.16g/1), $CaCl_2.2H_2O$ (0.375g/1 for MPLM and 0.188g/1 for RVD), $NaHCO_3$ (2.1g/1), $MgSO_4.7H_2O$ (0.29g/1) and glucose (2g/1). The buffer was gassed with 95% O_2, 5% CO_2.

Krebs solution for the mouse vas deferens (MVD) preparation was as above, but with the omission of $MgSO_4.7H_2O$ (Ward *et al.*, 1986, J. Pharmacol. Exp. Ther., 238, 625-634). Krebs/HEPES buffer was made up as Krebs buffer (above) with HEPES at a concentration of 25mM adjusted to pH 7.4 with 0.88M ammonia solution.

Methods

Ligand binding assays

Brain homogenates

Brains were removed from male CSI mice (discarding the cerebellum) and homogenised in Tris buffer (50mM, pH 7.4) at 10% tissue w/v. The homogenate was centrifuged at 25,500g for 20 mins. The supernatant was discarded and the pellet resuspended in buffer. The suspension was incubated at 37°C for 30 mins, then recentrifuged. The pellet obtained was resuspended in buffer to obtain a 1:60 tissue w/v ratio. This dilution corresponds to a protein concentration of approximately 1mg/ml as determined by Lowry's method (Lowry *et al.*, 1951, J. Biol. Chem., 193, 265-275).

For saturation binding assays tubes were set up containing 20µl of tritiated ligand and 960µl of brain homogenate in a total volume of 1ml. 20µl of naloxone (10µM) was added to each tube to determine the non-specific binding. For competition assays tubes contained labelled ligand (usually 1.0nM final concentration) plus increasing concentrations of competing cold ligand, or 20µl of water or 20µl of naloxone (10µM), which represented the total bound ligand and non-specifically bound ligand values respectively. Assay tubes were incubated at 25°C for 40 mins, unless stated otherwise. At

the end of the incubation period the tube contents were filtered through glass filter papers (Whatman GFB) which were presoaked in either Tris buffer pH 7.4 or Tris-buffer pH 7.4 containing polyethyleneimine (0.1%) to reduce non-specific binding to filters. The tubes were washed three times with 3ml of ice cold Tris buffer and the washings were also filtered. The filters were placed in scintillation vials, ecoscint scintillant fluid added, and the filters soaked for 8 hours. The radioactivity remaining on the filters was counted in a Minaxi Tricarb 4000 Series Liquid Scintillation Counter at an efficiency of 58%.

Binding parameters K_D and B_{max} were obtained using the LIGAND programme, following Scatchard analysis using the EBDA programme (McPherson, 1985, J. Pharmacol. Meth., 14, 213-228). IC_{50} values for competing ligands were determined using a logistic curve fitting programme developed by Barlow (1991, Ash Lea Cottage, Ravenstonedale, Kirkby Stephen, Cumbria. Foundations of pharmacology-computer curve fitting programme, publisher, Barton 1991).

Isolated tissue studies

Tissue preparation

a) **Guinea-pig myenteric plexus-longitudinal muscle (MPLM) bioassay**

Male Dunkin-Hartley guinea-pigs (400-500g) were killed by cervical dislocation. The ileum was removed and immediately placed inaerated Krebs solution at room temperature (Ward *et al.*, 1986, J. Pharmacol. Exp. Ther., 238, 625-634). After flushing out the contents, strips of myenteric plexus longitudinal muscle (MPLM) were removed and mounted, under a tension of 1g, in 3ml organ baths previously coated with silicon to reduce adsorption of peptides onto the glass surface. Tissues were bathed in Krebs solution at 37°C, aerated with 5% CO_2 in 95% O_2. After allowing a recovery period of 1 h, each tissue was stimulated through platinum ring electrodes using square wave pulses at supramaximal voltage at a frequency of 0.16Hz and a pulse width of 400μs.

b) **Mouse vas deferens (MVD) preparation**

Male CSI mice (930-50g), were killed by cervical dislocation. The vasa deferentia were removed immediately, and mounted under a tension of 0.5g in 1.8ml organ baths, previously coated with silicon to reduce adsorption losses of peptides. Tissues were bathed in Krebs without $MgSO_4$ at 37°C, aerated with 5% CO_2 in 95% O_2. After allowing a recovery period of 1 h, each vas deferens was stimulated through platinum ring electrodes

using a train of 3 square wave pulses of 1ms duration and 250ms delay at supramaximal voltage at a frequency of 0.1Hz.

Experimental

For all *in vitro* preparations the same procedure was performed as follows:-

a) **Agonist potencies**

Agonists were added to the organ baths in a cumulative way such that when the response to any one dose reached a maximum the next dose was administered, until approximately 80% inhibition of twitch height was attained after about four cumulative doses. The tissues were washed by overflow with Krebs solution until the original twitch height was restored. The potency of agonists was assessed by measurement of IC_{50}'s, the concentration of agonist causing 50% inhibition of the electrically evoked twitch.

b) **Antagonist affinities**

Antagonists were preincubated with the appropriate tissue for 15 mins, prior to the addition of an agonist. Dose-response curves for agonists were obtained before the addition of an antagonist and then repeated in the presence of varying concentrations of the antagonist (normally 10, 30, 100nM)> Dose-ratios were calculated at 50% inhibition and Schild plots constructed. Antagonists were removed from the tissue by continuous washing until the response to the added agonist was fully recovered. In some experiments antagonist Ke values were calculated using a single-dose method. The antagonist equilibrium dissociation constant (Ke) is a measure of affinity and was determined for a partial agonist in the rat vas deferens by pre-incubating the test compound for 15 mins and observing the effect on the dose-response curve for the full μ agonist DAMGO. Antagonist equilibrium dissociation constants (Ke) were obtained by analysing the results according to Kosterlitz and Watt (1968, Br. J. Pharmacol. Chemother., 33, 266-276).

Results

Opioid Receptor Profile - Morphine and morphine-6-glucuronide

The purpose of this experiment was to test analogues of morphine-6-glucuronide for their selectivity for different opioid binding sites. Ligands which have relative selectivity for different opioid binding sites are well known. The affinities of some illustrative compounds, DAMGO ([D-Ala^2, $MePhe^4$,Gly-ol^5]encephalin, DPDPE ([D- Pen^2,D-Pen^5]encephalin) and U69593 which have high affinities and are selective for

the opioid μ-, δ-, and κ- binding sites respectively are shown in Table 1 below:

Table 1: Affinities of opiates and specific ligands at mu, delta and kappa binding sites in mouse brain homogenates.

	Ki (nM)		
Compound	μ	δ	κ
morphine	6.22 ± 0.86	218.0 ± 41.2	84.7 ± 4.01
morphine-6-glucuronide	7.90 ± 1.48	75.1 ± 15.6	850 ± 118
morphine-3-glucuronide	> 10,000	> 10,000	> 10,000
DAMGO	2.45 ± 0.40	423.0 ± 7.9	1267 ± 265
DPDPE	> 10,000	4.76 ± 1.44	600 ± 124
U69593	> 10,000	> 10,000	2.51 ± 1.22

At the 3 opioid binding sites, morphine and M6G demonstrate the highest affinity for, and are approximately equipotent at, the μ-site (Table 1). The profile of morphine and M6G affinities differ, however, at the δ- and κ- sites, M6G being approximately 3-fold more potent at δ-sites and 10-fold less potent at κ- sites than morphine.

The actions of morphine and M6G on 2 isolated tissue preparations, namely the guinea-pig myenteric plexus-longitudinal muscle (MPLM) and the mouse vas deferens (MVD) are shown in Table 2. M6G is slightly more potent than morphine (approximately 2-fold) in both preparations. Also on both isolated tissues, the concentration of naloxone required to antagonise morphine and M6G to the same degree Ke) is equivalent and similar to that required to antagonise the selective μ-receptor ligand DAMGO (approximate Ke) naloxone = 3nM in each case). Thus the agonists actions of morphine and M6G on the MPLM and MVD are due to actions at the μ-receptor in both isolated tissue preparations. Relatively higher concentrations of naloxone are required to antagonise δ-mediated effects (DPDPE on the MVD, Ke naloxone = 20.4nM) and κ-mediated effects (U69593 on the MPLM. Ke naloxone = 9.0nM).

Table 2: Against p tencies and antagonism by naloxone in the m use vas deferens (MVD) and guinea-pig myenteric plexus-longitudinal muscle (MPLM) preparations.

	MPLM		MVD	
Compound	**K_{50}/nM**	**Ke(Nx)/$_n$M**	**K_{50}/nM**	**Ke(Nx)/$_n$M**
morphine	130.0 ± 7.2	3.45 ± 0.59	173.4 ± 62.8	3.60 ± 0.80
M-6-G	58.0 ± 4.3	3.00 ± 0.80	104.2 ± 17.1	2.61 ± 0.90
DAMGO	11.8 ± 1.2	1.60 ± 0.06	24.7 ± 3.0	1.90 ± 0.60
DPDPE	NT	NT	2.80 ± 0.63	20.4 ± 2.6
U69593	2.20 ± 0.41	9.00 ± 2.11	NT	NT

NT = not tested

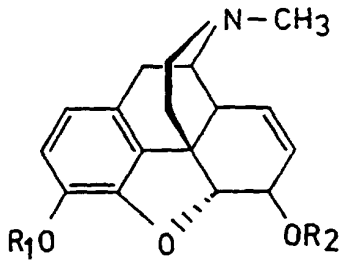
<u>Morphine-6-glucuronide analogues</u>

<u>Opioid Binding Site Affinities</u>

Analogues were tested and selected to at least retain and preferably exaggerate the relative binding profiles of M6G compared to morphine, i.e. equivalent, high affinity at μ-sites. and decreased affinity at κ-sites. Initially, 6-substituted codeine derivatives (i.e. with a 3-OMe function) were investigated as target compounds. Such derivatives, e.g. 3-OMe, 6-phthalate (BTG 2379) were shown to have low affinity for μ-binding sites (Ki=4500nM, Table 3). 3-silylmorphine (BTG 2381), however, itself retained a high affinity for μ-sites (Ki=2.5nM) and 3-silyl compounds were used as preparative intermediates for 6-substituted

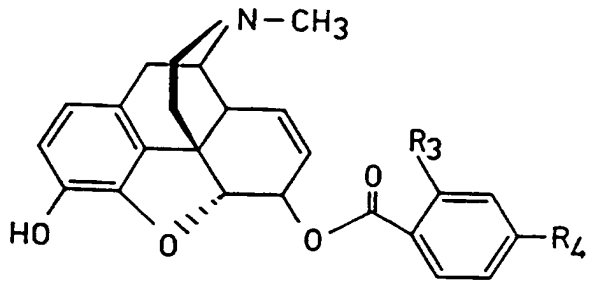
analogues. The addition of an aromatic ring at the 6-position, particularly phthalate (BTG 2382) and to a lesser extent benzoate (BTG 2383), further beneficially modified the binding profile. Table 3 below shows that BTG 2382 and BTG 2383 retained affinity at μ-binding sites (Ki = 17.5 and 310nM respectively), whilst losing κ-binding activity (Ki = > 10,000nM) and retaining δ-activity, in the case of BTG 2382 the affinity at the δ-site being in fact enhanced markedly (Ki = 4.1nM, Table 3). Analogues with 6-phthalate and 6-benzoate substitutions were investigated, therefore, returning to desilylated, morphine based structures (i.e. 3-OH). As with the protected series and shown in Table 4, the 6-phthalate ester of morphine (BTG 2403) retained good affinity at the μ-binding site (Ki = 27.8nM), slightly higher affinity at the δ-binding site (14.2nM) and low affinity at the κ-binding site (Ki = 2774nM). A series of para substituted 6-benzoate analogues (Table 4) demonstrated that the 6-(p-nitrobenzoate) ester (BTG 2404) showed a related profile with again good affinity at the μ-binding site (Ki = 30.1nM), slightly lower affinity at the δ-binding site (Ki = 68.5nM), but no demonstrable affinity at the κ-binding site, at least up to 10,000nM. The 6-(p-hydroxybenzoate) ester (BTG 2408) also displayed a related profile with high affinity at the μ-site (Kiμ = 1.7nM, Kiδ = 22.2nM, Kiκ = 157nM; Table 4). Morphine-6-phthalate (BTG 2403), morphine-6-(p-nitrobenzoate) (BTG 2404) and morphine-6-(p-hydroxybenzoate) (BTG 2408), therefore, all extend the differences in binding profile seen in M6G compared to morphine; all 5 compounds having μ-affinity in the 1-30nM range, with δ-affinities, ranging from morphine of 218nM to BTG 2403 of 14.2nM, and κ-affinity, ranging from morphine of 84.7nM to BTG 2404 of >10,000nM.

Table 3: Affinity of 3,6-substituted morphine derivatives at mu, delta and kappa binding sites in mouse brain homogenates.



			Ki (nM)		
Compound BTG	**R_1**	**R_2**	**μ**	**δ**	**κ**
morphine	H	H	6.22 ± 0.86	218.0 ± 41	84.7 ± 4.0
codeine	M_e	H	2700± 3.02	NT	NT
2379	M_e	phthalate	4500± 513	NT	NT
2381	silyl	H	2.50 ± 0.41	175 ± 6	135 ± 14
2382	silyl	phthalate	17.5 ± 2.8	4.1 ± 0.3	>10,000
2383	silyl	benzoate	310 ± 22	485 ± 25	>10,000

Table 4: Affinity of 6-substituted morphine derivatives at mu, delta and kappa binding sites in mouse brain homogenates.



			Ki (nM)		
Compound BTG	**R_3**	**R_4**	**μ**	**δ**	**κ**
morphine			6.22 ± 0.86	218.0 ± 41.2	84.7 ± 4.0
M-6-G			7.90 ± 1.48	75.1 ± 15.6	850 ± 118
2403	COOH	H	27.8 ± 3.8	14.2 ± 2.9	2774 ± 205
2404	H	NO_2	30.1 ± 1.4	68 ± 4.6	>10,000
2405	H	F	16.6 ± 3.2	83.3 ± 6.8	193.2 ±14.1
2406	H	Cl	17.7± 2.8	84.9 ± 8.4	149.9 ±12.2
2407	H	Br	28.4± 5.2	205.0 ±10.2	832.9 ±24.1
2408	H	OH	1.73± 0.26	22.2 ± 3.4	157.0 ±12.6

Opioid activity on isolated tissues

The above series of 6-substituted morphine derivatives was tested for activity on the isolated tissue preparations described previously. The results are shown in Table 5.

Table 5: Potencies of 6-substituted morphine derivatives in the guinea-pig MPLM and mouse vas deferens (MVD) preparations.

		IC_{50} nM	
Compound BTG	**6-substitution**	**MPLM**	**MVD**
morphine	H	130.0 ± 7.2	173.4 ± 62.8
M-6-G	glucuronide	58.0 ± 4.3	104.2 ± 17.1
2403	phthalate	350 ± 25	24.3 ± 3.5
2404	p-NO_2-bz	132 ± 12	1166 ± 467
2405	p-F-bz	1010 ± 102	1325 ± 262
2406	p-Cl-bz	1506 ± 161	1162 ± 151
2407	p-Br-bz	1800 ± 183	1281 ± 186
2408	p-OH-bz	9004 ± 106	230 ± 18

As discussed previously, although M6G has a slightly higher affinity in brain homogenate preparations for δ-binding sites compared to morphine (approximately 3-fold increase), on a relevant isolated tissue preparation, the mouse vas deferens (MVD), the potency difference is small (approximately 1.7-fold). Studies with the opioid antagonist naloxone on the MVD show that M6G, like morphine, is still acting via μ- and not δ-receptors in this tissue.

It was of interest, therefore, to investigate whether representative examples of the 6-substituted analogues with high δ-binding affinity in mouse brain homogenates were exerting their agonist effects on the MVD through μ- or δ-receptors in this isolated tissue. 3 compounds were studied, 3-silylmorphine-6-phthalate (BTG 2382, Ki δ binding = 4.1nM), morphine-6-(p-nitrobenzoate) (BTG 2404, Ki δ binding = 68.5nM) and morphine-6-(p-hydroxybenzoate (BTG 2408, Ki δ binding 22.2nM). The respective IC_{50}s of these compounds on the MVD were 41nM, 1166nM and 230nM. As shown in Table 6, the Ke's for antagonism by naloxone of BTG 2382, BTG 2404 and BTG 2408 were similar and in the range 14.9 - 20.2 nM. The concentrations of naloxone required for

antagonism of the analogues are considerably higher (approximately 6-7 times) and in marked contrast to that required for equivalent antagonism by naloxone of morphine and M6G (Ke naloxone = 3.6nM and 2.6nM respectively).

Thus, whereas in the MVD isolated tissue preparation morphine and M6G act via μ-receptors, the 6-substituted morphine analogues tested acted on this tissue via δ-receptors.

As may be expected, on the guinea-pig ileum myenteric plexus-longitudinal muscle (MPLM) preparation which lacks functional δ-receptors, naloxone antagonism of all 5 compounds showed similar Ke's (range 3.0 - 4.1 nM) indicating their action on this tissue is via μ-receptors.

Table 6: Antagonism by naloxone of morphine and derivatives on the MPLM and MVD isolated tissue preparations.

Compound	Substitution		Ke naloxone nM		
BTG	3-	6-	MPLM	MVD	
morphine	OH	H	3.5 ± 0.6	μ 3.6 ± 0.8	μ
M-6-G	OH	glucuronide	3.0 ± 0.8	μ 2.6 ± 0.9	μ
2382	silyl	phthalate	4.1 ± 1.4	μ20.2 ± 3.0	δ
2404	OH	p-NO_2-bz	3.5 ± 0.3	μ14.9 ± 1.5	δ
2408	OH	p-OH-bz	3.2 ± 0.4	μ17.8 ± 1.9	δ

IN VIVO EXPERIMENTS :

EXAMPLE 4: GENERAL METHOD FOR ASSESSING THE ANTINOCICEPTIVE ACTIVITY OF COMPOUNDS OF THE INVENTION

The antinociceptive effects of morphine and morphine-6-glucuronide in animals (and analgesia in man) are well known. In the present studies, therefore, only one confirmatory study was carried out in the mouse tail-flick test which showed, by subcutaneous administration, morphine and morphine-6-glucuronide to be equipotent, ED_{50} = 2.2 gl/kg and 1.9 mg/kg respectively, see Table 5 below.

Male CSI mice (25.30 g) (University of Nottingham Medical School) were used in these experiments. Animals were housed in groups of twelve in a room with a temperature controlled at 20°C on a 12 hour light-dark cycle and with free access to food and water.

Compounds of the current invention morphine sulphate and related compounds or vehicle controls (saline with 0.25% carboxy- methylcellulose) were injected subcutaneously. Six control mice (injected with vehicle) and six test mice were used for each study. Where antagonists were used these were injected subcutaneously 15 minutes prior to the agonists.

Antinociceptive activity was determined by the mouse tail-immersion test as follows:

Prior to injection and at the stated times past injection the tail was immersed in warm water at 50°C. The time for withdrawal of the tail was recorded. Antinociception was determined by an increase in the time-latency to withdrawal. The cut-off time for non-responding animals was 10 seconds. The time to reach maximal analgesie was deduced and ED_{50} values obtained for each drug as a measure of potency. The same points were subtracted from the test points and the dose required to give 50% of the maximal tail-flick latency (ED_{50}) was deduced.

The results are shown in the following Tables.

Table 7: Antinociceptive activity of morphine-6-p-nitr benzoate and m rphine-6-phthalate in the mouse warm-water tail flick test

Compound	Tail-flick latency(s)	
Morphine-6-p-nitrobenzoate	***vehicle control***	***drug***
1 mg/kg	2.2 ± 0.4	2.6 ± 0.4
3 mg/kg	1.9 ± 0.2	2.7 ± 0.1
10 mg/kg	1.3 ± 0.2	2.1 ± 0.1
30 mg/kg	1.7 ± 0.1	5.0 ± 0.1*
Morphine-6-phthalate		
1 mg/kg	1.3 ± 0.1	2.3 ± 0.3
3 mg/kg	2.7 ± 0.2	5.5 ± 0.3*
10 mg/kg	1.7 ± 0.2	6.7 ± 0.3*
30 mg/kg	1.4 ± 0.2	8.2 ± 0.9*

Drugs were administered s.c. in saline containing 0.25% carboxylmethylcellulose and tail-flick latencies were measured at 50°C, 60 minutes later. There were six animals in each group *P<0.05 (Wilcoxon signed rank test).

Table 8: Time course of the antinociceptive activity of morphine-6-p-nitrobenzoate (10 mg/kg s.c.) and morphine-6-phthalate (10 mg/kg s.c.) in the mouse warm-water tail-flick test

	Tail-flick latency (s)		
Time (mins)	*vehicle control*	*morphine-6-p-nitrobenzoate*	*morphine-6-phthalate*
-15	2.5 ± 0.2	1.9 ± 0.2	2.3 ± 0.2
15	2.8 ± 0.3	2.8 ± 0.5	3.0 ± 0.4
30	3.2 ± 0.4	5.3 ± 0.5*	4.6 ± 0.3*
60	2.9 ± 0.3	7.3 ± 1.0*	5.9 ± 0.5*
90	3.0 ± 0.3	8.9 ± 0.9*	6.2 ± 0.6*
120	2.8 ± 0.2	8.4 ± 0.8*	7.0 ± 0.5*
240	2.6 ± 0.2	4.1 ± 0.9*	3.4 ± 0.3*
360	2.3 ± 0.2	2.2 ± 0.3	2.1 ± 0.2

Drugs were administered s.c. in saline containing 0.25% carboxymethylcellulose and tail-flick latencies determined at 50°C at the stated times. There were 6 mice in each group. *P<0.05 (Wilcoxon signed rank test).

Discussion

Tables 7 and 8 show dose-related antinociceptive activities of the morphine-6-phthalate (BTG 2403) and morphine-6-p-nitrobenzoate (BTG 2404) on subcutaneous administration in the mouse tail-flick assay. BTG 2403 was slightly more potent than BTG 2404, IC_{50}s being 2.6 mg/kg and 16.2 mg/kg respectively.

Data from similar experiments with morphine (5 mg/kg and morphine-6-glucuronide were compared. The results are shown in Tables 9 and 10 below.

Table 9: Time Course Experiment f the antinociceptive activity of m rphine, 5mg/kg s.c. and morphine-6-glucuronide (M6G) 5mg/kg s.c. in the mouse warm water flick tail test

Time (mins)	Vehicle Control	Morphine-treated	Vehicle Control	M6G treated
-15	2.2 ± 0.3	2.1 ± 0.2	2.6 ± 0.3	1.8 ± 0.3
15	2.6 ± 0.4	8.5 ± 0.6 *	3.6 ± 0.5	7.6 ± 1.2 *
30	3.8 ± 0.3	9.8 ± 0.2 *	2.9 ± 0.4	10 *
60	2.9 ± 0.2	10 *	3.4 ± 0.3	10 *
90	2.7 ± 0.2	9.8 ± 0.2 *	2.8 ± 0.3	10 *
120	3.0 ± 0.2	7.9 ± 0.5 *	3.0 ± 0.2	10 *
240	2.7 ± 0.2	4.9 ± 0.6 *	3.0 ± 0.2	10 *
360	2.8 ± 0.2	2.7 ± 0.2	2.5 ± 0.2	10 *
540	NT	NT	2.5 ± 0.2	7.1 ± 0.9 *
720	NT	NT	1.8 ± 0.2	3.2 ± 0.5 *
1440	NT	NT	1.8 ± 0.1	2.0 ± 0.4

NT = not tested

Drug was administered s.c. (sub-cutaneously) in saline and tail flick latencies (50° water) determined at the stated times. A cut-off time of 10 seconds was used. There were six mice in each group * $P < 0.05$ (Wilcoxon signed rank test).

Table 10 : Dose effect resp nses for the antinociceptive effect of morphine and morphine-6-glucuronide (M6G) in the mouse warm water tail-flick test

	Tail flick latency (seconds)	
Compound mg/kg	**Morphine**	**M6G**
0	2.4 ± 0.3	2.3 ± 0.1
0.3	3.5 ± 0.4 *	3.4 ± 0.3 *
1.0	3.9 ± 0.4 *	3.8 ± 0.5 *
3.0	7.0 ± 1.0 *	9.2 ± 0.6 *
5.0	10 *	10 *
10.0	10 *	10 *

Drug was administered in saline, subcutaneously, using 6 mice for each concentration. Tail flick latencies were determined 60 minutes after injection using 50°C water. A cut-off time of 10 seconds was used.

* Represents $P < 0.05$ (Wilcoxon signed rank test)

Peak antinociceptive activity with BTG 2403 and BTG 2404 (120 minutes and 90 minutes) was delayed compared to that of morphine (60 minutes) and activity by all 3 compounds had returned to control levels 360 minutes after subcutaneous administration.

With an extension of the profile of the 6-substituted analogues in binding and *in vitro* studies demonstrating increased affinity and actions mediated by the δ-receptor, one compound, the 6-phthalate ester of morphine (BTG 2403), was tested for δ-mediated effects in an antinociceptive test, the mouse tail-flick. Results are shown in Table 11. Morphine (5mg/kg) and BTG 2403 (30mg/kg), administered subcutaneously, demonstrated approximately equivalent antinociceptive effects. The selective δ-receptor antagonist naltrindole (1mg/kg sc) completely antagonised the effects of BTG 2403, but had no effect on those induced by morphine. BTG 2403 would appear to exert antinociceptive effects via δ-opioid receptors.

Table 11: Effect of naltrindole (1 mg/kg) on the antinociceptive activity f morphine (5 mg/kg) and morphine-6-phthalate (30 mg/kg) in the mouse warm-water tail-flick test

Treatment	*Tail-flick latency(s)*
pre-test	2.0 ± 0.3
vehicle	2.3 ± 0.2
naltrindole	2.2 ± 0.2
morphine	10.0 (cut-off)*
morphine + naltrindole	10.0 (cut-off)*
morphine-6-phthalate	9.8 ± 0.2*
morphine-6-phthalate + naltrindole	2.5 ± 0.3

Drugs were administered subcutaneously in saline containing 0.25% carboxymethylcellulose and tail-flick latencies were determined at 50°C 90 minutes (morphine) or 120 minutes (morphine-6-phthalate) later. Naltrindole was administered 15 minutes prior to the agonists. *$P<0.05$ (Wilcoxon signed rank test).

EXAMPLE 5: ANTINOCICEPTIVE EFFECTS OF MORPHINE AND DERIVATIVES

ORAL ANALGESIC STUDY:- PAW LICKING TEST IN MICE

Male, LACA mice (Tucks), weighing between 30-40g, were dosed orally with the vehicle or compound, 1 h prior to the sub-plantar injection of 10 µl of 5% formalin. The duration of paw licking was measured 0-5 min and 15-30 min after formalin administration.

The vehicle was 0.25% carboxymethylcellulose in 0.9% saline and solutions were sonicated and shaken prior to administration; this was especially necessary for the high concentrations of the two test compounds (morphine-6-phthalate and morphine-6-p-nitrobenzoate).

All experiments were performed between 1400-1700h and in any one experiment at least one control animal and three of the compounds were studied.

Animals were removed from the animal house at 1300h and the temperature of the behavioural room was noted (it did not exceed 25°C although several of the experiments were performed when the outside temperature was 30-35°C).

The duration of licking in the treated groups was compared with that of the controls using one-way ANOVA followed by the Dunnett Multiple Comparison Test. A non-parametric test (Kruskal-Wallis, followed by Dunn's Multiple Comparison Test) was also used as there was some concern about the normal distribution of the values. Calculations were performed through the INSTAT programme.

The results are shown in Table 12 below

Table 12: Antinociceptive effects of morphine and derivatives

		Antinociceptive effect	
Compound BTG	***6-substitution***	***tail-flick ED_{50} mg/kg sc***	***paw-lick lowest dose * po***
morphine	OH	2.2 ± 0.3	10.0
M6G	glucuronide	1.9 ± 0.3	No effect at 80
2403	phthalate	2.6 ± 0.4	40.0
2404	p-NO_2-bz	16.2± 2.6	40.0

* lowest dose producing a statistically significant ($p < 0.05$) antinociceptive effect.

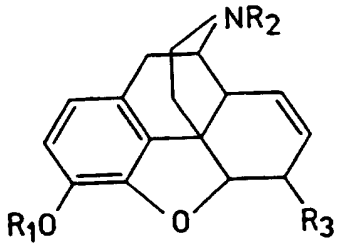
Morphine induced, dose related antinociceptive effects were observed at doses of 10 mg/kg and higher. In comparison, morphine-6-glucuronide failed to induce statistically significant antinociceptive effects at any dose tested (10-80 mg/kg po). BTG 2403 and BTG 2404 (both at 40 mg/kg) induced antinociceptive effects on oral administration although dose related effects with a highest dose were demonstrated only with the latter compound.

Both the 6-substituted aromatic analogues, therefore showed statistically significant oral antinociceptive effects, the compound being slightly less potent than morphine, but more potent than morphine-6-glucuronide, which failed to demonstrate antinociceptive effects, even at the highest dose tested.

5

CLAIMS

1. A compound of Formula I



wherein R_1 = H (morphine analogue), CH_3 (codeine analogue)

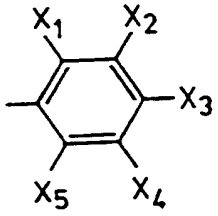
R_2 = H, alkyl group of 1 to 4 carbon atoms, allyl, cyclopropylmethyl

R_3 = a group $-O-\overset{O}{\overset{\|}{C}}-R_4$

$-O-CH_2-R_4$ (ether)

$-O-COCH = CHR_4$ (cinnamate)

R_4 =



wherein X_1, X_2, X_3, X_4 and X_5 which may be the same or different are separately selected from H, alkyl of 1 to 4 carbon atoms, NH_2, NO_2 alkoxy group of 1 to 4 carbon atoms, hydroxy, halogen, N-alkyl, group of 1 to 4 carbon atoms, morpholine, or a group COR_5 wherein R_5 is H, OH, O-alkyl where alkyl is from 1 to 4 carbon atoms, or one of X_1 and X_2, X_2 and X_3, X_3 and X_4 or X_4 and X_5 together with an alkylene group optionally interrupted by O, S or N of up to 5 atoms in length complete a ring and a pharmaceutically acceptable salt thereof for use in therapy.

2. A compound according to Claim 1, wherein R_2 is H or alkyl group of 1-4 carbon atoms or pharmaceutically acceptable salts thereof.

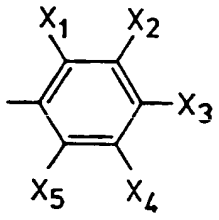
3. A compound according to Claim 2, wherein the alkyl group is methyl or pharmaceutically acceptable salts thereof.

4. A compound according to Claim 1, 2 or 3 wherein

$$R_3 = -O-\overset{\overset{O}{\|}}{C}-R_4$$

or pharmaceutically acceptable salts thereof.

5. A compound according to any preceding claim wherein R_4 is



wherein X_1, X_2, X_3, X_4 and X_5 which may be the same or different are separately selected from H, NH_2, NO_2, OH, halogen or COR_5 wherein R_5 is OH or pharmaceutically acceptable salts thereof.

6. A compound according to Claim 5, wherein at least 3 of X_1, X_2, X_3, X_4 and X_5 are H or pharmaceutically acceptable salts thereof.

7. A compound according to Claim 5 or 6, wherein when there is only one substituent, the X substituent is in the para position or when there is more than one substituent, one is in the para position or pharmaceutically acceptable salts thereof.

8. A compound according to Claim 1 which is morphine or codeine-6-nitrobenzoate or pharmaceutically acceptable salts thereof.

9. A compound according to Claim 1 which is morphine or codeine-6-phthalate or pharmaceutically acceptable salts thereof.

10. A process for making a compound of Formula I which are ethers defined in Claim 1 which comprises the reaction of codeine or morphine with the appropriate alkyl chloride in the presence of sodium hydride in THF.

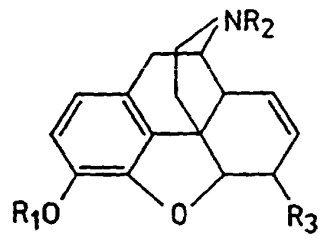
11. A pharmaceutical composition comprising a compound of Formula I as defined in any of Claims 1-11 together with a pharmaceutically acceptable diluent or carrier.

12. A pharmaceutical composition according to Claim 11 adapted for oral administration.

13. A pharmaceutical composition according to Claim 11 adapted for parenteral administration.

14. A pharmaceutical composition according to Claim 11 adapted for delayed release.

15. A compound of Formula II



wherein

R_1 = H (morphine analogue), CH_3 (codeine analogue)

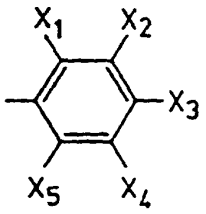
R_2 = H, alkyl group of 1 to 4 carbon atoms, allyl, cyclopropylmethyl

R_3 = a group $-O-\overset{O}{\overset{\|}{C}}-R_4$

$-O-CH_2-R_4$ (ether)

$-O-COCH = CHR_4$ (cinnamate)

wherein R_4 =



wherein X_1, X_2, X_3, X_4 and X_5 which may be the same or different are separately selected from H, an alkyl group of 1 to 4 carbon atoms, NH_2, NO_2, alkoxy group of 1 to 4 carbon atoms, hydroxy, halogen, N-alkyl group of 1 to 4 carbon atoms, morpholine, a group COR_5 wherein R_5 is H, OH, O-alkyl where alkyl is from 1 to 4 carbon atoms, or one of X_1 and X_2, X_2 and X_3, X_3 and X_4 or X_4 and X_5 together with an alkylene group optionally interrupted by O, S or N of up to 5 atoms in length complete a ring with the proviso that not all X_1, X_2, X_3, X_4 and X_5 are hydrogen and pharmaceutically acceptable salts thereof.

16. The use of a compound according to any one of Claims 1-10 or Claim 15 for the manufacture of a medicament for use in the alleviation of pain.

17. A method of alleviating pain in an individual comprising administering a therapeutically effective amount of a compound according to any one of Claims 1-10 or Claim 15 to the individual.

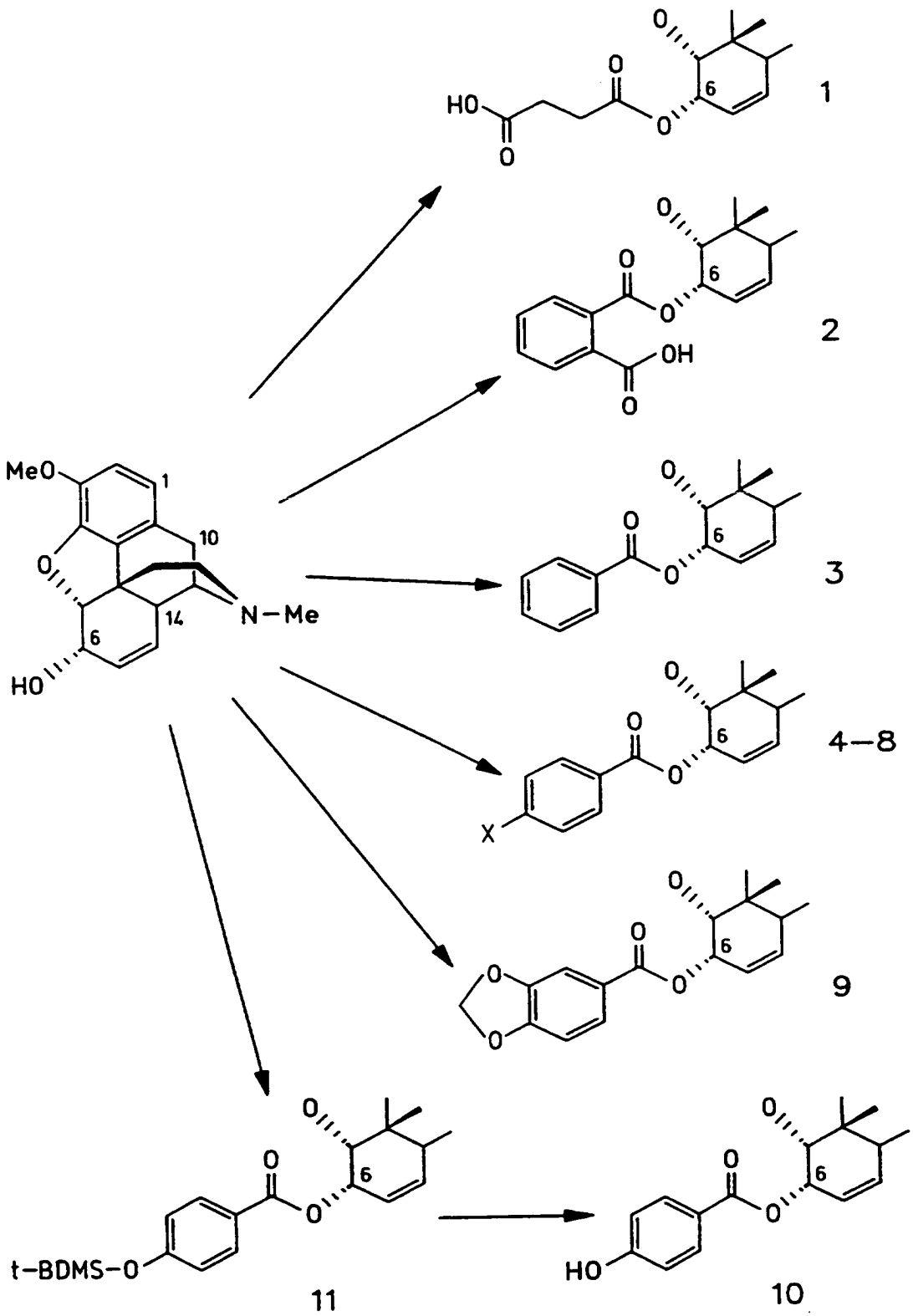


Fig.1

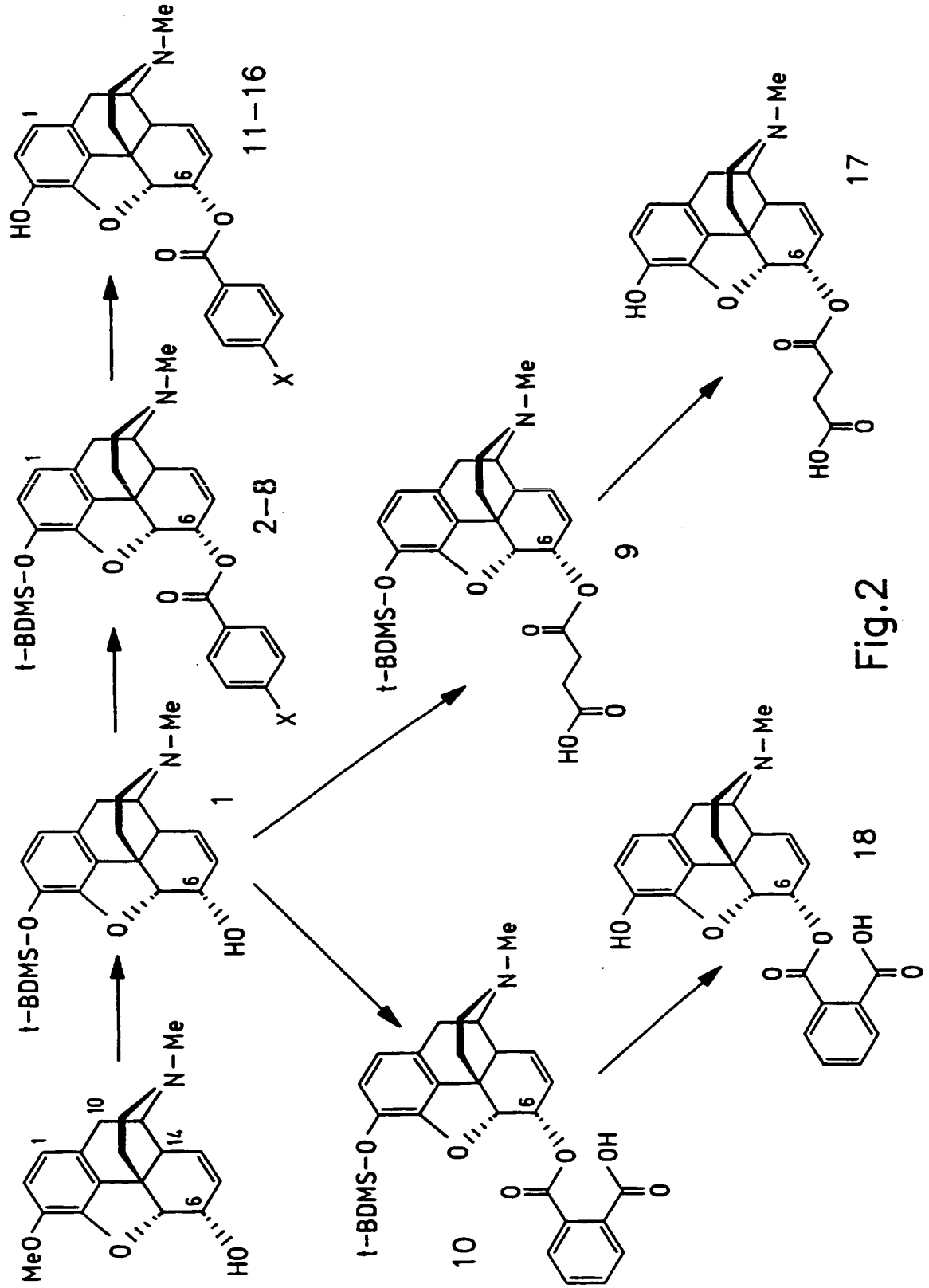


Fig.2